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Average Daily Change in SARS-Cov-2 Reverse Transcription Polymerase Chain Reaction Thresholds among Elderly Patients with COVID-19: A Basis for the Proposed Determination of Isolation Periods

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Abstract

After a cluster of coronavirus disease 2019 (COVID-19) due to nosocomial infection occurred among elderly patients, I suspected that the isolation period for COVID-19 might be too short to protect patients and staff members. This study attempted to define an appropriate isolation period to minimize the risk of disease transmission. Nineteen patients contracted COVID-19 during an outbreak at the General Medicine Ward of Saitama Memorial Hospital, Japan, between July and August 2022. One patient died soon after the infection. For the remaining 18 patients, daily changes (Δ) in cycle threshold (CT) values were calculated using severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reverse transcription polymerase chain reaction testing, which was performed at least twice. The isolation release date was based on data when the CT value reached 30, using Δ of the CT values. The isolation periods ranged from 8 to 32 days (median: 15.5 days). Isolation lasted for 25–32 days in three patients. In conclusion, the conventional isolation period of 10 days plus symptom-based extra days after onset appears to be too short to prevent nosocomial SARS-CoV-2 infection among the elderly. It would be necessary to define the isolation period based on the average Δ in CT values.

Keywords: COVID-19; SARS-Cov-2 RT-PCR; Cycle Threshold Value; Isolation Period; Nosocomial Infection

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; family Coronaviridae, genus Beta coronavirus, species Severe acute respiratory syndrome-related coronavirus) is the causative agent of coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has become a major public healthcare threat with real-world societal and economic consequences.

At a hospital in the suburb of the New Metropolitan Saitama City near Tokyo, Japan, inpatients with COVID-19 were successfully treated without incurring nosocomial infection. However, in the summer of 2022, a moderate scale of infection clusters, including 19 patients and 15 staff members, was encountered in the hospital ward. For the prevention of nosocomial infections, Clinical Management of Patients with COVID-19 guidelines proposed by the Ministry of Health, Labor and Welfare of the Japanese Government were strictly followed [1]. Despite the observance of these regulations, including the commonplace use of personal protective equipment to control risks at work, intrahospital COVID-19 infections occurred.

The major reason for this failure was the unprecedented infectivity of the SARS-CoV-2 Omicron variants [2]. Another reason may be related to the management of patients after infection. Since April 2020 >130 patients with COVID-19 have been admitted, treated, and released after the 10 days plus symptom-based extra days of isolation, which has been the quarantine period recommended by the above-mentioned guidelines [1]. Following the release from isolation, most of the patients spent several days or weeks undergoing further treatment in a room with patients who did not have COVID-19. The hospital staff members attended to the post-isolation patients wearing a mask but without complete personal preventive equipment. When confronted with an infection cluster, the cycle threshold (CT) value of one patient who was released from isolation 12 days after symptom onset and had been staying in rooms with other COVID-free patients was 19.2 at 20 days after onset, far below 30, the least infectivity

level of SARS-CoV-2 [3-5]. Thus, it was suspected that infectious virus shedding might have occurred even after deisolation. In other words, the isolation period might have been too short to protect other patients as well as staff members.

Almost all data used to derive an "adequate" isolation period were from the general population. Under special circumstances, for example, in hospitals treating elderly patients with advanced cancer, intractable pneumonia, or other severe illnesses, adequate quarantine may differ from conventional quarantine [6]. This issue seems to be critical when dealing with the extremely infectious Omicron variants.

Infectivity of SARS-CoV-2 has been known to depend on the viral load, which is assessed by the CT value [4]. Therefore, this study aimed to investigate the CT values of SARS-CoV-2 RNA in elderly patients who contracted COVID-19 during an outbreak of nosocomial infection at the hospital. The daily change in CT values was calculated and applied to determine the "adequate" period of quarantine.

Patients and Methods

Nineteen patients (9 men and 10 women, mean age 79.9 years, range 67–89 years) contracted COVID-19 consecutively between July 24 and August 20, 2022 at the General Medicine Ward of Saitama Memorial Hospital, Saitama, Japan. None of the patients were suspected of having been infected by SARS-CoV-2 before contraction. The patients were receiving treatment for rheumatoid arthritis, pneumonia, diabetes mellitus, terminal stage cancer, and other diseases.

The patients who presented with an unexpected fever immediately underwent a rapid antigen test (QuickNavi™-COVID19 Ag, Denka KK, Gosen, Niigata, Japan) or a nucleic acid amplification test (NAAT) (ID NOW™ New Coronavirus 2019, Abbott Diagnostics Medical KK, Matsudo, Chiba, Japan). Those who tested positive underwent reverse transcriptase quantitative polymerase chain reaction (RT-PCR) for SARS-CoV-2 to determine the CT value as described below.

SARS-CoV-2 RT-PCR was performed by BML, INC., Saitama, Japan. The patients' nasopharyngeal swab specimens were transferred to the laboratory under cold conditions within 6 hours. The RT-PCR assay was performed on the platform of Amplitude Solution (Thermo Fisher Scientific, Waltham, MA, USA) using TaqPath SARS-CoV-2 Real-time PCR Detection kit HT [7] (Thermo Fisher Scientific) according to the manufacturer's instructions to detect SARS-CoV-2-specific ORF1ab-, S-, and N-genes. Once detected, a CT value was obtained for each gene. In all positive cases, ORF1ab- and N-genes were consistently detected and showed similar CT values, whereas S-gene was never detected. The CT values of N-gene were used in this study.

For patients who tested positive in a rapid test, the other patients in the same room received the same test as quickly as possible to determine the presence or absence of COVID-19. All patients with a positive result were isolated for COVID-19 treatment. The patients who tested negative were designated as the "close contact group" and isolated for 5 days in another room. Among individuals who tested negative initially, two tested positive 8 and 19 days later, respectively. During isolation, three patients died of progression of the underlying diseases, possibly aggravated by concomitant COVID-19.

The SARS-CoV-2 gene alterations in all these cases were consistent with Omicron BA.5: positive ORF1ab, positive N, and negative S genes. **Table 1** shows the demographic characteristics of the 19 patients, including information on underlying diseases, nutritional methods, therapeutic drugs against SARS-CoV-2, number of vaccinations, and a history of COVID-19.

All patients with COVID-19, except the one who died soon after diagnosis, underwent at least two RT-PCR tests to determine the CT values of the N-gene. The first RT-PCR test was performed as soon as possible when the patient tested positive on a rapid antigen or NAAT. The second test was performed 10 days after symptom onset or 7–10 days after the first test, according to the timing when COVID-19 was first detected.

Based on the change in CT values per day (Δ1-2), the date when the CT value reached 30 was estimated, as shown in **Table 2**. A CT value of >30 indicates the loss of SARS-CoV-2 infectivity, according to various studies [3-5, 8]. Four patients had CT values in the second test that were too low to judge the date of release. In such cases, a third RT-PCR test was performed 7–9 days later. The daily average change (Δ2-3) and the date of release were calculated again. One patient underwent a fourth test 5 days later for re-estimation of the daily change Δ3-4 and date of release. No patient needed more than four tests.

The study was conducted according to the Declaration of Helsinki. Informed consent for participation in this study was obtained from all patients or their legal representatives. The Ethics Committee of Saitama Memorial Hospital approved the study (Approval No. 202204).

Results

In 18 patients, the Δ1-2 ranged from −0.558 to 1.843, with a mean (standard deviation) of 0.940 (0.636) (Table 1). In five of these patients, Δ1-2 was <0.5. One of the five patients had a negative CT value (−0.558) and died 15 days after illness onset. The other four were released from isolation ≥18 days (median: 25 days) after symptom onset. One patient with Δ1-2 of 0.75 died at 15 days after onset, before release from isolation.

Four patients underwent a third SARS-CoV-2 RT-PCR test to obtain Δ2-3 values, which ranged from 0.157 to >3.314 (median = 1.312). In all four patients, Δ2-3 was larger than Δ1-2. Only one patient underwent a fourth test to obtain Δ3-4. In this patient, Δ1-2, Δ2-3, and Δ3-4 were <0.5, and the isolation period lasted for 32 days.

In 10 patients in the current study, the CT values, which were measured 10 days after onset, ranged from 12.7 to 33.1, with a median of 22.45. Only two of the 10 patients had a CT value ≥29.9.

The isolation period for the available 16 patients in the current series ranged from 8 to 32 days, with a median of 15.5 days.

Table 1. Demographic characteristics of the patients in the study.

No	Age (years)/ sex	Main diseases (a)	Treatment for main diseases (b)	Alimentation (c)	VAC/COVID-19-related history (d)	COVID-19-related signs	COVID-19-related drugs (e)	CT values (days after symptom onset or positivity onset) (f)				Daily average change (Δ) in CT values (g)			isolation peiod (days after symptom onset or positivity onset) (h)
								CT1	CT2	CT3	CT4	Δ1-2	Δ2-3	Δ3-4	
1	85/F	RA/Pn	PSL/AB	NGT/PN	×3 (21)	fever	REM	9.9 (3)							death on 8
2	68/F	knee Fx postop	rehabilitation	oral	×3 (20)	none	none	24.0 (0)	30.1 (7)			0.871			8
3	81/M	HCC	supportive	oral	×3 (13)	none	none	26.4 (0)	30.3 (7)			0.557			8
4	75/F	Pn	AB	PN	×3 (22)	fever	REM	16.0 (3)	28.9 (10)			1.843			11
5	81/F	DM	insulin	oral	×3 (24)	none	MOL	18.2 (3)	29.9 (10)			1.671			11
6	78/M	UTI	AB	oral	×2 (15)	fever	REM	15.7 (1)	25.1 (9)			1.175			13
7	73/F	foot Fx postop	rehabilitation	oral	×3 (21)	none	MOL	18.2 (2)	33.1 (10)			1.863			13
8	87/M	SDH postop	supportive	oral	×3 (23)	fever	REM	10.2 (1)	24.0 (10)			1.533			14
9	83/F	RA/Pn	TCL/AB	oral	×3 (23)	fever	MOL+REM	15.6 (4)	20.1 (10)			0.75			death on 15
10	84/F	bladder CA	supportive	oral+PVI	×3 (25)	fever	MOL	19.4 (-1)	12.7 (10)			-0.56			death on 15
11	75/F	AD	supportive	oral	×3 (19)	fever	MOL	10.7 (1)	21.6 (9)			1.363			15
12	67/M	AD	supportive	GTF	×2 (18)/ COVID-19 (47)	fever	MOL	11.8 (0)	23.5 (10)			1.17			16
13	80/M	PD/Tx	supportive	GTF	×3 (19)	fever	MOL	9.2 (1)	24.9 (13)			1.308			17
14	71/M	DM/Pn/CKD	insulin/AB	oral+PVI	none	fever	REM	9.4 (0)	21.4 (10)			1.2			17
15	87/F	CKD/HF	supportive	oral+PVI	×2 (52)/ COVID-19 (21)	none	MOL	13.8 (3)	21.1 (10)			1.043			19
16	86/M	DM/UTI/AD	insulin/AB	oral	×2 (6)	fever	REM	13.7 (1)	16.8 (10)	>40 (17)		0.344	>3.314		18
17	83/F	pneumonitis	PSL/AB	oral	×3 (17)	none	MOL	9.6 (2)	10.9 (11)	23.2 (20)		0.144	1.367		25
18	89/M	AD/PMI	supportive	oral	none	fever	MOL	20.2 (8)	22.0 (17)	30.8 (24)		0.2	1.257		25
19	85/M	DM/SIADH	insulin/NaCl	oral	×3 (21)	fever	MOL	18.1 (0)	22.9 (11)	24.0 (18)	26.1 (23)	0.436	0.157	0.42	32

(a) RA: rheumatoid arthritis Pn: pneumonia, HCC: hepatocellular cell cancer, DM: diabetes mellitus, UTI: urinary tract infection, SDH: subdural hematoma CA: cancer, AD: Alzheimer's disease PD: Parkinson's disease, TX: tracheostomy, CKD: Chronic kidney disease. HF: heart failure, PMI: Pace maker implementation, SIADH: syndrome of inappropriate antidiuretic hormone secretion.

(b) PSL: prednisolone, AB:M antibiotics, TCL: tacrolimus, NaCl: sodium chloride

(c) NGT: nasogastric tube feeding, PN: Parenteral nutrition, GTF: Gastrostomy tube feeding, PVI: peripheral venous infusion

(d) Number of doses of corona virus 2019 (COVID-19) vaccination (VAC) / previous COVID-19 infection: weeks from the last vaccination or infection

(e) REM: remdesivir intravenously, MOL: molnupiravir peroally or per tube

(f) (g) (h) see table 2 for details

Table 2. Calculation of the average daily change (Δ) in cycle threshold (CT) and determination of the isolation release day.

		Average daily change (Δ) in CT	Determination of the isolation release day after onset
Usually			
CT1 (day x1) = a1	CT2 (day x2) = a2	Δ1-2 = (a2-a1)/(x2-x1)	x2 + (30 - a2)/Δ1-2
If Δ1-2 is too low to estimate isolation release day			
CT2 (day x2) = a2	CT3 (day x3) = a3	Δ2-3 = (a3-a2)/(x3-x2)	x3 + (30 - a3)/Δ2-3
If Δ2-3 is still too low to estimate isolation release day			
CT3 (day x3) = a3	CT4 (day x4) = a4	Δ3-4 = (a4-a3)/(x4-x3)	x4 + (30 - a4)/Δ3-4

Discussion

The isolation period for patients with COVID-19 has been discussed since its emergence. With increasing knowledge of epidemiology, as well as advances in diagnostic and therapeutic measurements, the isolation period is becoming increasingly shorter than before. In recent times, if patients with COVID-19 experience symptom relief for several days, release from isolation at 10 days after onset plus extra days depending on symptoms has been recommended, and the Japanese government has observed the same policy [1]. Considering the current knowledge about COVID-19 and the Omicron variant, the Centers for Disease Control and Prevention (CDC) in the United States shortened the recommended time to 5 days for the general population without

symptoms or with resolving symptoms [9].

Whether the recommended isolation period is 5 or 10 days, these guidelines are considered to be for the general population. The criteria for the isolation period may differ in people with severe comorbidities or in those with moderate-to-severe illness.

Some researchers have used the CT values of SARS-CoV-2 RT-PCR to elucidate the infectivity of SARS-CoV-2 and applied the data to determine the isolation period. CT values are known to represent the viral load. The CT value is not an absolute marker of infectivity and depends on PCR methods and equipment. However, patients with CT values of >30 are considered the least likely to have infectious disease form [4, 10-12].

We adopted the theory that CT values of >30 could be a marker for isolation release and applied it to determine period of isolation. SARS-CoV-2 RT-PCR was performed at two or more time points, the average daily change (Δ) in CT values was calculated, and date of isolation release was determined.

The most outstanding finding in the current study was a marked difference in ΔCT values in elderly patients. This difference may be due to underlying disorders and/or medication modifications. Therefore, it is important to investigate at least two CT values on different days in the same patient. A third or fourth test would be required in some cases, as seen in 4 of the 16 patients enrolled in this study, excluding the 3 patients who died.

CT values have been used to predict the prognosis or mortality of COVID-19 pneumonia [8, 13-15]. Several authors have argued that CT values are useful for determining isolation periods [3-5] However, few studies seem to have specifically and prospectively demonstrated how and when a patient with COVID-19 should be released from isolation in terms of nosocomial infection risk management. Aranha et al. [4] suggested that isolation of COVID-19 patients with CT values >30 could be shorter to facilitate adequate space in COVID-19 care centers and reduce the burden on the healthcare infrastructure. Alshukairi et al. [16] investigated CT values and viral cultures in 13 immunocompromised patients and recommended that a risk-based approach for infectious viral shedding in immunocompromised patients would be useful to identify those who should be quarantined for >20 days. For symptomatic and "moderately and severely immunocompromised" patients, the CDC recently recommended a test-based strategy including fever resolution, symptom improvement, and two consecutive negative tests (antigen test or NAAT) [17]. However, the presence or absence or degree of the immunocompromised state remains unclear.

The method of calculation of the daily average change and estimation of isolation periods in this study seem objective and can be applied to patients with or without an immunocompromised status.

The isolation periods in this study were longer than conventionally recommended periods. In three patients, isolation lasted for 25–32 days. Although extremely long isolation periods were required in a small number of the patients, it is important to identify those who would continue to infect the immunologically weak patients.

A limitation of this study is derived from the theory that CT values of >30 could be a marker of the least infectivity of SARS-CoV-2. However, this theory has not been thoroughly examined. Further basic and clinical research is required to verify, deny, or modify the theory. Another limitation may be the validity of determining the isolation periods by setting the date of release based on a CT value of 30. There is need to await the results of further studies on nosocomial infection prevention in hospitals or nursing homes.

In conclusion, the conventional isolation period of 10 days after onset seems too short to prevent nosocomial SARS-CoV-2 among the elderly. It would be necessary to define isolation periods based on the average daily change in CT values.

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Conflict of Interest

The author declares that there is no conflict of interest.

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