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Note

Could threshold cycle value correctly reflect the severity of novel coronavirus disease 2019 (COVID-19)?*  
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A novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], which initially appeared in December 2019 in Wuhan, China, 1–3 rapidly spread to many countries, resulting in the pandemic of the novel coronavirus disease 2019 (COVID-19). This pandemic caused health problems of human beings and an economic decline worldwide. Although the novel coronavirus (SARS-CoV-2) could cause severe viral pneumonia and acute respiratory distress syndrome (ARDS), showing a high mortality rate of 12–45% among patients requiring ICU admission, most patients are asymptomatic or have very mild to moderate symptoms [1–3].

It is considered that cycle threshold value (Ct-value) of real-time reverse transcription (rRT)-polymerase chain reaction (PCR) assay is correlated with viral load and the positive result of rRT-PCR testing could be infectious and the negative result is not [4]. The Japanese Ministry of Health, Labour and Welfare set the discharge criteria to be two consecutive negative results of SARS-CoV-2 rRT-PCR in throat or nasopharyngeal swabs from COVID-19 patients. While rRT-PCR by a nasopharyngeal swab is effective for diagnosis of COVID-19 [5], we wonder if the result could correctly reflect the disease severity and infectiousness to others. We experienced some COVID-19 cases which were asymptomatic and had persistent positive nasopharyngeal SARS-CoV2 rRT-PCR for 10–20 days. We reviewed COVID-19 patients admitted to our institute for examining the correlation between Ct-value of SARS CoV2-rRT-PCR and the severity and activity of COVID-19. This is the first report documenting that Ct-value of rRT-PCR could not reflect the disease severity and activity of COVID-19. This study was approved by the Institutional Review Board of Aichi Medical University Hospital.

We present 10 cases of COVID-19 (7 pneumonia and 3 non-pneumonia) as shown in Table 1. The median age of the patients was 48 years (range 16–92 years). For all, 6 (60%) were males.

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Seven patients had pneumonia, while 3 patients did not. Nine (90%) survived and 1 (10%) died. We classified the patients with COVID-19 into 2 groups as follows: pneumonia (case 1–7) and non-pneumonia (8–10) group.

Comparing the 2 groups, there were no statistical differences of the initial Ct-values [Mean ± standard deviation (SD) 20.3 ± 5.5 v.s. 21.7 ± 5.9, p = 0.733 by student-t test] and re-checked Ct-values (Mean ± SD 28.9 ± 8.3 v.s. 24.1 ± 4.3, p = 0.414 by student-t test). Re-check of nasopharyngeal SARS-CoV2 rRT-PCR was performed when the patients improved in all cases. Initial Ct-values are not correlated with the duration of hospital stay.

Fig. 1 shows correlation between Ct-values and days after symptoms onset among COVID-19 patients. After day 8, Ct-values in all cases decreased to 25–30 except for one death case (case 7). However, some cases could have a Ct-value of <45, showing a positive result of SARS-CoV2-rRT-PCR even though the patients were asymptomatic. Interestingly, although case 2 (pneumonia case), 8 and 9 (non-pneumonia cases) were asymptomatic for 13–19 days, their rRT-PCR results kept on being positive. Although case 7 had received favipiravir as the initial treatment, his condition deteriorated, resulting in death on day 12. The family members of the patient did not want him to receive an aggressive treatment such as tocilizumab due to his age and dementia. His deterioration might have been influenced by IIP.

According to current discharge criteria, a lot of asymptomatic COVID-19 patients have to stay in hospitals. A long duration of admission among patients with COVID-19 who are asymptomatic could contribute to the increase of medical costs and medical staffs’ workload. Depending on the area, there may even be a lack of beds for patients who require intensive care in Japan. A previous report documented that Ct-value of influenza virus and RS virus was effective to evaluate the disease severity [6]. The result suggests that Ct-values decrease as patients recover while some of them remain positive (Table 2).

### Table 1

| Patients’ characteristics and clinical outcomes (Ct-value and disease severity). |
|---|---|---|---|---|---|---|---|
| Cases | Age | Sex | Past history | Initial Ct-value | Re-checked Ct-value | Pneumonia | Duration of admission (days) | ICU admission | Treatment | Outcome |
| 1 | 56 | M | Hypertension | 18 | 32.2 | Yes | 17 | No | Ciclesonide, Camostat, Favipiravir | Survival |
| 2 | 55 | F | None | 22 | 22.1 | Yes | 18 | No | Ciclesonide, Camostat | Survival |
| 3 | 16 | F | None | 27 | 29.6 | Yes | 8 | No | Ciclesonide, Camostat | Survival |
| 4 | 48 | M | None | 27 | 45 | Yes | 15 | Yes | Ciclesonide | Survival |
| 5 | 22 | M | None | 16 | 29.4 | Yes | 7 | No | Ciclesonide, Camostat, Favipiravir | Survival |
| 6 | 50 | M | DM, HTN, Hepatic disease | 18 | 28 | Yes | 11 | No | Ciclesonide, Favipiravir | Survival |
| 7 | 92 | M | Dementia, IIP | 14 | 16 | Yes | 12 | No | Favipiravir | Death |
| 8 | 25 | M | None | 22 | 24.5 | No | 14 | No | Ciclesonide, Camostat | Survival |
| 9 | 63 | F | RA | 16 | 19.6 | No | 23 | No | Favipiravir | Survival |
| 10 | 48 | F | None | 27 | 28.2 | No | 13 | No | Ciclesonide, Camostat | Survival |

Ct-value, cycle threshold value; DM, diabetes mellitus; HTN, hypertension; IIP, idiopathic interstitial pneumonia; ICU, intensive care unit; RA, rheumatoid arthritis; M, male; F, female.

* The patient was treated due to the age and underlying disease.

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Fig. 1. Shows that Ct-values detected by RT–PCR in nasopharyngeal swabs from COVID-19 patients.
The infectiousness may decline significantly 8 days after symptom onset, as live virus could no longer be cultured [7,8]. In our cases, 7/10 patients showed an increase of Ct-values >25 on day 8 after symptom onset. The patients needed another 8 days on average after re-check rRT-PCR until discharge.

Although it is important to prevent secondary transmitted infection, the current problem is that asymptomatic patients occupy beds in hospitals in Japan, resulting in the lack of hospital beds which may hamper the admission of needy COVID-19 patients who have respiratory symptoms. According to the study in Taiwan, no secondary transmission was observed among 91 close contacts of the 9 asymptomatic cases [9]. The study suggested that most transmission of COVID-19 occurred at the very early stage of the disease or even before the onset of symptoms, and the secondary clinical attack rate among contacts decreased over time as symptoms developed and progressed [9]. Thus, we do not think that asymptomatic patients need to stay hospitalized after their symptoms improved even when the result of rRT-PCR remains to be positive. To prevent medical collapse, the discharge criteria for COVID-19 patients by negative result of SARS-CoV-2 rRT-PCR should be reconsidered.

There were several limitations in this report. First, this is a retrospective study in a small sample size. Thus, there might be a bias in the data selection and analysis. Second, we analyzed only COVID-19 patients with a positive rRT-PCR result from a nasopharyngeal swab. There might have been a technical error when the test was performed. Third, we did not analyze correlation between Ct-value and the infectiousness of COVID-19 in this study.

We conclude that Ct-values of real-time RT-PCR assay decrease as the patients recover, while some of them remain positive although the patients were asymptomatic. Positive results of rRT-PCR for SARS-CoV2 might not always correlate with the degree of infectiousness. The discharge criteria by rRT-PCR testing might have contributed to a COVID-19 patients’ long term hospitalization and should be reconsidered.

Author contributions

Contributor Mikamo H was responsible for the organization and coordination of the trial. Asai N was the chief investigator and responsible for the data analysis. Asai N and Sakanashi D developed the trial design. Asai N, Koizumi Y, Kishino T, Yamagishi Y, Shiota A and Mikamo H contributed to collect the specimen collecting and transportation. Sakanashi D, Nakamura A, Yamada A, Ohno T, Miyazaki N, Kawamoto Y Suematsu H, and Koita I contributed to perform rRT-PCR. Asai N, Kato H, Hagihara M and Ohashi W contributed for statistical analyses. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

All co-authors have none declared.

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