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The first eleven cases of SARS-CoV-2 Omicron variant infection in Japan: A focus on viral dynamics

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant has spread rapidly worldwide. We report the clinical characteristics and threshold cycle (Ct) values of the first 11 patients infected with the SARS-CoV-2 Omicron variant in Japan. All patients were younger returnees from abroad; 10 patients had received two doses of vaccine. Estimated Ct values for the 11 patients were 6.0 (95% confidence interval [CI] 4.2-7.3) days for > 30, 10.6 (95% CI 9.5-11.9) days for > 35, 15.1 (95% CI 13.6-17.6) days for > 40, and 19.7 (95% CI 17.3-23.7) days for > 45. Our results provide important insights for indicators of infection control.

***Keywords*:** COVID-19, B.1.1.529, threshold cycle, characteristics

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 variant, subsequently named Omicron, was first identified in South Africa on 24 November 2021 (*1*). It has spread rapidly, with 11,148 confirmed cases worldwide as of 18 December 2021 (*2*). In Japan, the first case of SARS-CoV-2 Omicron variant infection was reported on 30 November 2021 in a man returning from Namibia (*3*). Although there is increasing information concerning the genetic and molecular characteristics of the Omicron variant, there remains limited information regarding its clinical characteristics and viral dynamics. Here, we describe the clinical characteristics and threshold cycle (Ct) values of the first 11 cases of SARS-CoV-2 Omicron variant infection reported in Japan.

Setting and patients

This study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM) (Approval no. NCGM-G-003472-02). Written consent for participation in the study was obtained from all patients. This retrospective cohort study of patients with SARS-CoV-2 Omicron variant was conducted between November and December 2021 at the NCGM (Tokyo, Japan), an infectious disease reference centre with approximately 780 hospital beds.

Demographic and clinical characteristics

The following information was collected from medical charts: characteristics and comorbidities; risky behaviour including travel history; vaccination; symptoms at admission, body temperature, supplementary oxygen, and treatment; and imaging findings.

In total, 11 patients with SARS-CoV-2 Omicron variant infection were examined in this study. The median (range) age was 39 (1-64) years; 10 patients (90.9%) were male. All patients had been diagnosed after travelling abroad; eight (72.7%) were from Africa, while one (9.1%) each was from Europe, North America, and Latin America. All but one paediatric patient had received two doses of vaccine: seven had received mRNA-1273 (Moderna) and three had received BNT162b2 (Pfizer-BioNTech). Three patients (27.3%) had comorbidities: two had hypertension (18.2%), and one (9.1%) each had hyperlipidaemia and diabetes mellitus. The most common symptoms were fever and sore throat (n = 5, 45.5%), followed by cough (n = 4, 36.4%) and fatigue (n = 1, 9.1%). No patients exhibited pneumonia or required supplementary oxygen (Table 1).

Table 1. Characteristics of 11 cases of SARS-CoV-2 Omicron variant infection

Characteristics	Values
Age	39 [1-64][a]
Male sex	10 (90.9)[b]
Body mass index	23.8 [22.0-26.4][c]
Smoking	0 (0, two ex-smokers)
Travel history	11 (100)
	Africa 8 (72.7)
	Europe 1 (9.1)
	North America 1 (9.1)
	Latin America 1 (9.1)
Risky behaviour within 14 days before symptom onset	
Close contact	3 (27.3)
Eating with other people	0 (0)
No avoidance of three Cs[d]	0 (0)
Asymptomatic infection	3 (27.3)
Days from onset to admission	2 [2-3]
Past history of COVID-19	0 (0)
Vaccination	
None	1 (9.1)
1 dose	0 (0)
2 doses	10 (90.9)
	Moderna 7 (70.0)
	Pfizer 3 (30.0)
Comorbidities	
Hypertension	2 (18.2)
Hyperlipidaemia	1 (9.1)
Diabetes mellitus	1 (9.1)
Maximum body temperature	37.0 [36.5-37.9]
Supplementary oxygen required	0 (0)
Pneumonia	0 (0)
Symptoms during admission	
Fever (≥ 37.5°C)	5 (45.5)
Cough	4 (36.4)
Sore throat	5 (45.5)
Headache	0 (0)
Fatigue	1 (9.1)
Difficulty breathing	0 (0)
Myalgia	0 (0)
Treatment during admission[e]	
Antivirals	0 (0)
Biologics	1 (9.1)
	Sotrovimab 1 (100)
Steroids	0 (0)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019. [a]Numbers here are median [range]. [b]Categorical variables are presented as absolute number (percentage).[c]Continuous variables are presented as median [interquartile range]. [d]Closed spaces with poor ventilation, Crowded places with many people nearby, and Close-contact setting (*e.g.*, close-range conversations). [e]Based on the clinical record until 18th December 2021. Eight of 11 patients remain hospitalised.

Laboratory analysis

Samples for mutational analysis were sent to the National Institute of Infectious Diseases for viral genome sequencing and confirmed to contain the Omicron variant (GISAID Accession 64 ID: EPI_ISL_6913953, 6914908, 7194610, 7860178, 7889643, 7889642, 7860189, 7860190, 7860188, 7860185, 7860184). All specimens used for the analysis of Ct values were collected by clinical staff with nasopharyngeal swabs after admission. Ct values were measured for the nucleocapsid N2 gene using Xpert® Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA, USA) (*4*). Associations of Ct values with days from symptom onset or diagnosis were examined by linear regression analysis. Fifty-seven polymerase chain reaction (PCR) test results from 11 patients were included in the analysis. The Ct values were positively correlated with days from symptom onset or diagnosis (Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=41*). An interval of 6.0 (95% confidence interval [CI] 4.2-7.3) days was needed for the Ct value to become greater than 30; additional intervals were 10.6 (95% CI 9.5-11.9) days for > 35, 15.1 (95% CI 13.6-17.6) days for > 40, and 19.7 (95% CI 17.3-23.7) days for > 45 (Figure 1, Figure S1, and S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=41*).

Discussion

The viral dynamics of SARS-CoV-2 vary according to variant type and patient vaccination status. For example, the Delta variant exhibits significantly lower Ct values at symptom onset and a slower decay rate, compared with the Alpha variant (*5*). To our knowledge, there are no reports concerning the trends of Ct values for SARS-CoV-2 Omicron variant. In this study, we investigated the changes in Ct values from the time of symptom onset or test positivity when reverse transcriptase (RT)-PCR was performed on nasopharyngeal swab specimens.

All 11 patients were diagnosed with SARS-CoV-2 infection during post-travel quarantine; eight of them were returnees from Africa. This quarantine is a component of the increased screening required by the Japanese government in the context of the Omicron variant. None of the patients were elderly; only three had comorbidities. This would be related the fact that all patients were overseas travellers. All but one patient (a 1-year-old child) had received two doses of vaccine (none received booster shots); thus, these 10 patients exhibited breakthrough infections. All patients were asymptomatic or had mild disease; however, they were hospitalised because Japanese Infectious Disease Control Act tentatively requires all patients with Omicron variant to be hospitalised and isolated. Although clinical outcomes have not been followed until discharge in eight patients, no patient has developed a severe respiratory condition or died. The clinical characteristics of the patients with SARS-CoV-2 Omicron variant infection in this study are consistent with the characteristics of such patients in the United States (most are younger, have been vaccinated, and exhibit mild disease) (*6*).

In this study, the estimated Ct values were > 30 at 6.0 (95% CI 4.2-7.3) days, > 35 at 10.6 (95% CI 9.5-11.9) days, > 40 at 15.1 (95% CI 13.6-17.6) days, and > 45 at 19.7 (95% CI 17.3-23.7) days. A study from England reported that in patients with coronavirus disease 2019 (COVID-19), Ct values gradually decrease during the first 10 days, then reach a plateau and remain positive (*7*). Additionally, a report from Italy regarding hospitalised patients with COVID-19 indicated that the time to PCR-

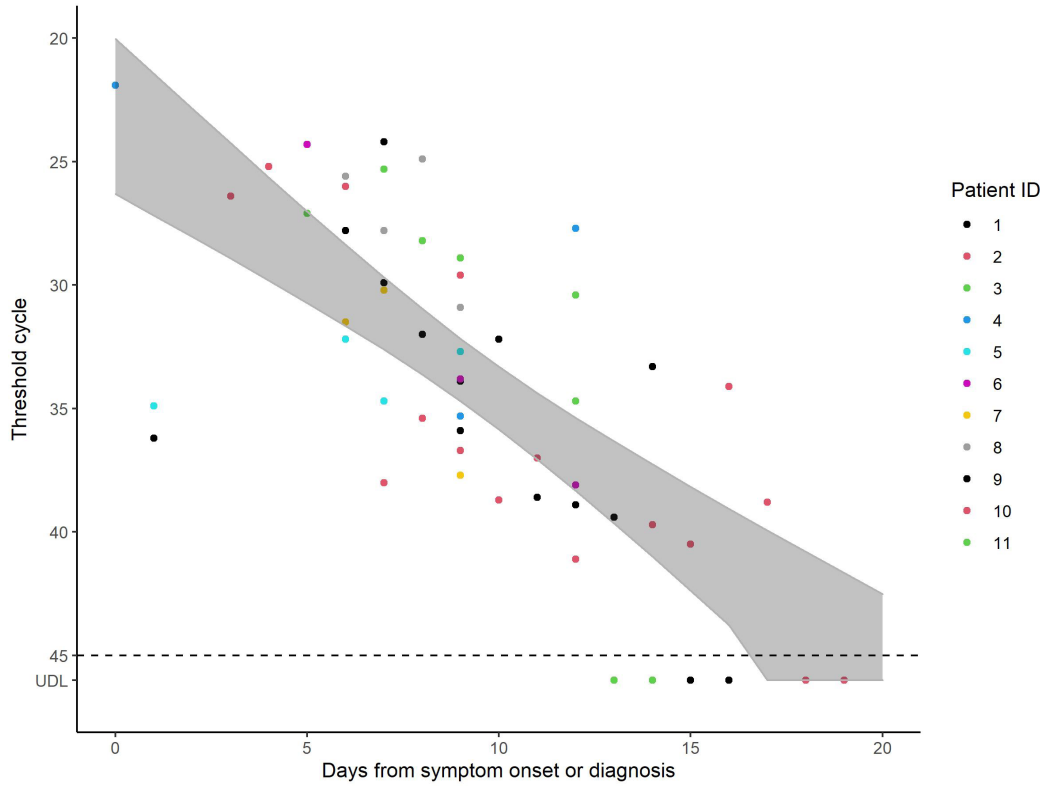

Figure 1. Detection of SARS-CoV-2 by RT-PCR targeting the nucleocapsid N2 gene. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; UDL: under detection limit; ID: identification. Shaded area represents 95% confidence interval of the predicted value of the liner model. Threshold cycle values > 45 were regarded as 45 because of the detection sensitivity limit. Threshold cycle values were measured for the nucleocapsid N2 gene using Xpert® Xpress SARS-CoV-2.

negativity was approximately 30 days (*8*). These studies were performed in patients infected with the original SARS-CoV-2 strain, before the introduction of the vaccine. In a French study of patients with COVID-19 (mainly caused by the SARS-CoV-2 Delta variant), regression analysis predicted that RT-PCR test results would remain positive for > 20 days for the Delta variant (*5*). In our analysis, 19.7 days were needed for the Ct value to become > 45. Although our analysis did not investigate the influences of factors other than the time from symptom onset or diagnosis, it might be valuable information for public health authority. Most patients had completed two doses of vaccinations, suggesting that the Omicron variant causes long-term virus excretion, despite full vaccination.

Because we did not attempt to isolate the virus, we could not evaluate its viability or infectivity. However, some studies have revealed relationships between Ct value and culture positivity findings. In separate studies by French, Canadian, and Japanese investigators, no cultures were obtained from samples with Ct ≥ 34, Ct > 24, and Ct > 30, respectively (*9-11*). Another study in England revealed the estimated probability of viral recovery from samples with Ct > 35 was 8.3% (*7*). Considering that samples with Ct values > 35 are unlikely to contain viable virus, our finding of Ct values > 35 in 10.6 (95% CI 9.5-11.9) days might be useful as an indicator for infection control.

Conclusions

In our investigation of the first 11 patients with Omicron variant infection in Japan, all were asymptomatic or had mild disease after travelling abroad. Assuming a linear association between Ct values and the days from symptom onset or diagnosis (with no other influencing factors), the estimated Ct values were > 30 at 6.0 (95% CI 4.2-7.3) days, > 35 at 10.6 (95% CI 9.5-11.9) days, > 40 at 15.1 (95% CI 13.6-17.6) days, and > 45 at 19.7 (95% CI 17.3-23.7) days. Our results provide important insights for indicators of infection control; further analysis of the relationships between Ct values and viral load will enable more robust control measures for the Omicron variant.

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