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Viral kinetics of SARS-CoV-2 in asymptomatic carriers and presymptomatic patients

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ABSTRACT

From a total of 71 laboratory-confirmed cases, three presymptomatic patients and 10 patients with entirely asymptomatic infections were identified. In two of the three incubation period patients, the viral titer in the presymptomatic period was very high (Ct value < 20). The median number of days to first negative RT-PCR in the asymptomatic carriers was 4.5 (range 2.5–9), and all asymptomatic carriers reached a first RT-PCR Ct > 35 within 14 days after diagnosis. Patients who have COVID-19 may already be infectious before there are symptoms, and 14 days of isolation after diagnosis may be sufficient in entirely asymptomatic cases.

An outbreak of a novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan, China in December 2019 (Lu et al., 2020). This outbreak went on to become a public health emergency of international concern. The World Health Organization defines coronavirus disease 2019 (COVID-19) as the infectious disease caused by laboratory-confirmed SARS-CoV-2, diagnosed by real-time reverse transcription polymerase chain reaction (RT-PCR) (WHO, 2020). COVID-19 can present as an asymptomatic carrier state, an acute respiratory disease, or as pneumonia.

Some studies have found that people infected with SARS-CoV-2 in the asymptomatic or presymptomatic period can be infectious (Bai et al., 2020; Mao et al., 2020). Current evidence on how long to quarantine asymptomatic carriers is limited. In a recent paper, Mao et al. reported reservations about the 14-day isolation period for asymptomatic carriers, because this period was based on observations of only two cases (Mao et al., 2020). The lack of isolation capacity in some countries is expected to lead to an explosive increase in COVID-19 cases. Here, we report the viral kinetics according to the absence or presence of symptoms.

This study included patients with laboratory-confirmed COVID-19 admitted to the Affiliated Hospitals of Chonnam National University between February 4 and April 7, 2020. RT-PCR was positive if the cycle threshold (Ct) values of both the envelope (E) and RNA-dependent RNA polymerase (RdRp) genes of SARS-CoV-2 were less than 35. Specimens were collected from all patients at least 2 days after hospitalization and physicians checked their symptoms and signs daily. Epidemiological and clinical information was obtained.

Seventy-one patients were hospitalized for treatment or isolation. Patients who had any of the following features at quarantine release were analyzed: (1) asymptomatic carrier ($n = 10$), i.e. those who had no symptoms in the 14 days preceding diagnosis until release from quarantine; (2) incubation period patients ($n = 3$), i.e., those who were asymptomatic during the 14 days preceding diagnosis, but became symptomatic during quarantine. Table 1 shows the clinical characteristics of the patients analyzed. The median age of the asymptomatic carriers was 31 years (interquartile range 17.8–55.8 years).

Three patients who were asymptomatic on admission developed myalgia, fever, and a cough 1 or 2 days afterwards, without pneumonia. In two of the three patients, the viral load during the incubation period was very high (Ct value < 20), but all patients first reached Ct > 35 by day 14 (Figure 1A). In the asymptomatic SARS-CoV-2 carriers, the viral load on admission was not relatively

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Table 1
Clinical characteristics of presymptomatic patients with mild symptoms and asymptomatic carriers

Patient	Age (years)	Sex	Underlying disease	Contact with confirmed COVID-19 case	Incubation period[a] (days)	Symptom-free period after admission (days)	Maximal O_2 supply (min/l)	Pneumonia extent (max 24)	Treatment
Incubation period patients with mild symptoms									
A	20	F	None	Family	N/A	2	0	0	LPV/r
B	30	M	None	Religious event	4	2	0	0	None
C	30	M	HTN	Religious event	4	1	0	0	None
Asymptomatic carriers					From contact to diagnosis (days)	From diagnosis to hospitalization (days)			
D	58	M	DM	Family	N/A	2	0	0	None
E	79	F	Asthma, osteoporosis	Medical care	10	7	0	0	None
F	8	F	None	Foreign visit, family	N/A	2	0	0	None
G	37	M	Liver donor	Foreign visit	14[b]	0	0	0	None
H	48	M	DM	Religious event	N/A	2	0	0	None
I	24	F	None	Religious event	20[b]	1	0	0	None
J	8	F	None	Family	N/A	2	0	0	None
K	21	M	None	Dormitory	14[b]	1	0	0	None
L	55	F	None	Occupational	10	7	0	0	None
M	25	F	None	Foreign visit	N/A	1	0	0	None

COVID-19, coronavirus disease; DM, diabetes mellitus; F, female; HTN, hypertension; M, male; N/A, not applicable; LPV/r, lopinavir/ritonavir.
[a] Incubation period: from contact to symptom onset (days).
[b] Patients G, I, and K: RT-PCR was performed to determine whether to terminate quarantine at 14 days after contact with a SARS-CoV-2 infected patient.

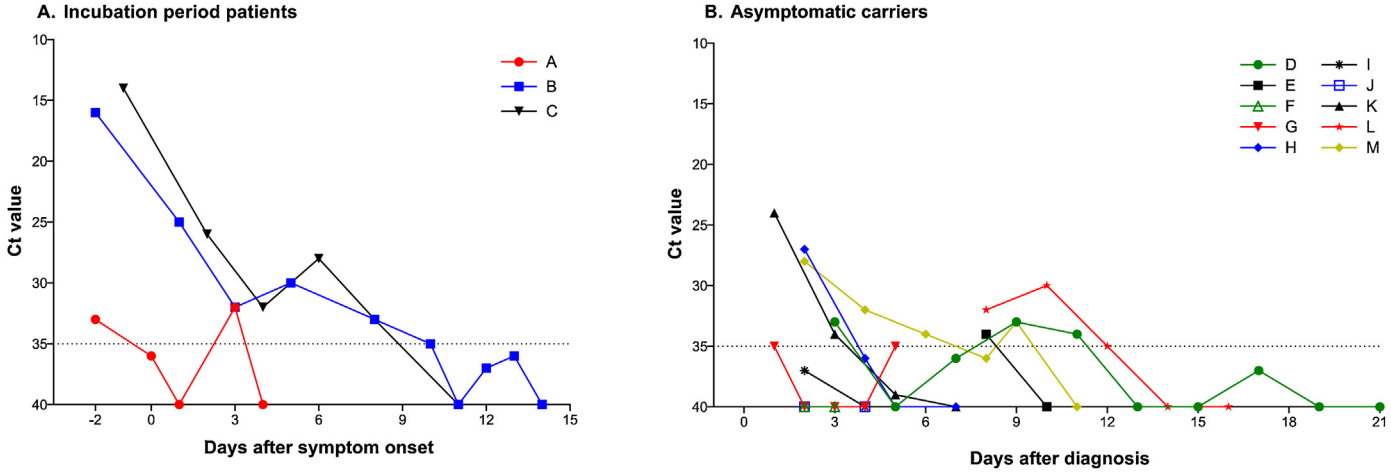

Figure 1. Viral load detected in nasal–throat swabs obtained from patients infected with SARS-CoV-2. The cycle threshold (Ct) values of the RNA-dependent RNA polymerase (RdRp) gene on reverse-transcriptase polymerase chain reaction (RT-PCR) assays of nasal–throat swabs obtained from (A) three incubation period patients with mild cases of COVID-19, and (B) 10 asymptomatic carriers. Ct = 35 is the cut-off for a positive result and Ct = 40 is a negative sample; Ct = 40 was the limit of detection.

high (Figure 1B). The median time to first RT-PCR Ct > 35 result after diagnosis in the asymptomatic carriers was 4.5 days (range 2.0–8.5 days) and all asymptomatic cases first reached a Ct > 35 within 14 days after diagnosis (Figure 1B).

It was found that RT-PCR was indeterminate or negative 14 days after diagnosis in entirely asymptomatic individuals who were not given any antiviral agents. Although the presence of viral RNA in specimens does not distinguish between infective and non-infective viruses, a study found that live virus could not be detected by culture in cases with Ct > 35 (Wolfel et al., 2020). Of 309 patients in a community treatment center cohort with mild symptoms in Korea, 101 (32.7%) had negative results at 4 days after admission, and 85 (27.5%) had negative results on secondary viral testing 8 days after admission (Park et al., 2020). On the other hand, in the study by Mao et al., PCR was positive on day 19 of isolation in patients receiving antiviral agents, which might have prolonged virus detection in the two asymptomatic carriers. A modelling study estimated that 18% would be true asymptomatic cases, including the incubation period (Mizumoto et al., 2020). If the percentage of asymptomatic carriers is large, the cost of isolation for public health management may be enormous. Our data suggest that 14 days of quarantine at home after diagnosis may be adequate in entirely asymptomatic carriers.

It was found that incubation period patients had high viral loads before the onset of symptoms, and that some asymptomatic carriers had an initial viral load that might be a living virus. Interestingly, this differs from the transmission of the virus causing SARS (SARS-CoV), which occurred mainly after days of illness (Lipsitch et al., 2003). On April 2, 2020, the Korea Center for Disease Control and Prevention (KCDC) guidelines for the public health management of COVID-19 patients updated its contact investigation from 1 day before symptom onset to 2 days before onset (KCDC, 2020). In the present study, it was found that there was a high viral load on RT-PCR at 2 days before symptom onset, which suggests a high risk of transmission.

In summary, patients who have COVID-19 may already be infectious when there are no symptoms, and 14 days of isolation may be sufficient in entirely asymptomatic cases. We expect that these results will assist infection control practices during this pandemic.

Declarations

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Ethical statement: The analysis of cases was approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No. CNUH-2020-039).

Conflict of interest: The authors declare that there is no conflict of interest.

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