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Patterns of viral clearance in the natural course of asymptomatic COVID-19: Comparison with symptomatic non-severe COVID-19

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ABSTRACT

Objectives: The aim of this study was to elucidate patterns of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance in the natural course of asymptomatic coronavirus disease 2019 (COVID-19).

Methods: Consecutive patients with non-severe COVID-19 were included retrospectively. Asymptomatic patients with a normal body temperature and no evidence of pneumonia throughout the disease course were assigned to the asymptomatic group. The reverse transcription PCR (RT-PCR) assay was repeated every two to five days after the first follow-up RT-PCR assay. Negative conversion was defined as two consecutive negative RT-PCR assay results within a 24-h interval. Rebound of the cycle threshold (Ct) value was defined as negative from the single RT-PCR assay and positive from the following assay.

Results: Among a total of 396 patients identified (median age 42.5 years (interquartile range (IQR) 25.0–55.0 years), 35.6% male), 68 (17.2%) were assigned to the asymptomatic group and 328 (82.8%) to the symptomatic group. The time until negative conversion was significantly shorter in the asymptomatic group than in the symptomatic group: median 14.5 days (IQR 11.0–21.0 days) and 18.0 days (IQR 15.0–22.0 days), respectively ($p = 0.001$). Rebound of Ct values was observed in 78 patients (19.7%).

Conclusions: Time until negative conversion is shorter in asymptomatic COVID-19 than in symptomatic COVID-19. Rebound of Ct values is not uncommon.

Introduction

The first cases of coronavirus disease 2019 (COVID-19) were reported in Wuhan, China in December 2019 (Chen et al., 2020; Huang et al., 2020). The pathogen has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lu et al., 2020; Zhu et al., 2020). COVID-19 has rapidly become widespread across the world. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. From the end of February through March 2020, Daegu—the fourth largest city in South Korea—was emerging as an epicenter of COVID-19 in South Korea. The government of South Korea recommended that all

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people who had been in contact with a patient with COVID-19 or had visited locations where outbreaks had occurred should be tested, even if they did not have symptoms. In the early phase of the outbreak, individuals who were diagnosed with COVID-19 were required to be hospitalized for quarantine, regardless of disease severity. As the number of patients increased, the hospitals started to run out of rooms. For this reason, asymptomatic and mildly symptomatic patients were quarantined in dedicated COVID-19 facilities and moderately to severely symptomatic patients were hospitalized in dedicated COVID-19 hospitals (Park et al., 2020; Choi et al., 2020).

The clinical features of COVID-19 range from asymptomatic to critical illness. Epidemiological surveys have shown evidence that SARS-CoV-2 can be contagious in the presymptomatic stages of COVID-19 (Rothe et al., 2020; Ye et al., 2020). Furthermore, it is known that persistently asymptomatic COVID-19 is transmissible (Bai et al., 2020). Cases of asymptomatic COVID-19 represent an emerging and serious public health issue given their elusive and contagious characteristics. However, patterns of SARS-CoV-2 clearance in asymptomatic COVID-19 remain unclear.

The aim of this study was to elucidate changes in results of real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 and the time until negative conversion in the natural course of asymptomatic COVID-19 compared with symptomatic non-severe COVID-19.

Methods

This was a retrospective cohort study. Consecutive patients of all ages who were hospitalized in one of two dedicated COVID-19 hospitals (Korea Workers' Compensation and Welfare Services Daegu Hospital and Chungju Medical Center) after the diagnosis of non-severe COVID-19 by real-time RT-PCR for SARS-CoV-2, performed on specimens from a nasopharyngeal swab between February 24 and April 2, 2020, were included retrospectively.

The severity of COVID-19 was defined using the current guidelines for the diagnosis and treatment of community-acquired pneumonia (Metlay et al., 2019). Patients with severe COVID-19 and patients in whom negative conversion was not confirmed were excluded. Patients with no COVID-19-related symptoms, a body temperature ≤37.4 °C, and no evidence of pneumonia based on chest X-rays throughout the disease course were assigned to the asymptomatic group. Patients with COVID-19-related symptoms, a body temperature ≥37.5 °C, or findings compatible with pneumonia based on chest X-rays or computed tomography (CT) were assigned to the symptomatic group. COVID-19-related symptoms included newly developed cough, sputum, sore throat, rhinorrhea, headache, chest pain, fever, chills, myalgia, dyspnea, anosmia, ageusia, and diarrhea.

Laboratory tests including complete blood cell count and blood chemistry were performed upon admission. Supportive care was given for the asymptomatic patients, while treatment for specific symptoms with or without antimicrobial therapy was provided for the symptomatic patients. Antimicrobial therapy included lopinavir/ritonavir, hydroxychloroquine, third-generation cephalosporin, and azithromycin.

During hospitalization, the first follow-up RT-PCR assay for SARS-CoV-2 was performed on specimens from a nasopharyngeal swab, 7 days after diagnosis for the asymptomatic patients and immediately after the disappearance of symptoms or improvement in pneumonia stage for the symptomatic patients. When the follow-up RT-PCR assay was negative, the following RT-PCR assay was performed on specimens from a nasopharyngeal swab after 24–48 h. When the follow-up RT-PCR assay was positive, the following RT-PCR assay was performed on specimens from a nasopharyngeal swab after two to five days.

For the patients hospitalized in the Korea Workers' Compensation and Welfare Services Daegu Hospital, RT-PCR assays for the *E* (envelop protein) and *RdRP* (RNA-dependent RNA polymerase) genes were performed with the PowerChek 2019-nCoV Assay (Kogene Biotech Inc., Seoul, South Korea) in a Bio-Rad CFX96 Deep Well real-time PCR detection system (Bio-Rad, Hercules, CA, USA), after viral RNA extraction using an NX-48 viral nucleic acid extraction kit (Genolution, Seoul, South Korea) in conjunction with Nextractor NX-48 (Genolution) at Samkwang Medical Laboratories. A positive test result was defined as a well-defined exponential fluorescence curve that crossed the threshold (cycle threshold (Ct) value) at ≤35 cycles for the *E* genes or the *RdRP* genes, respectively.

For the patients hospitalized in Chungju Medical Center, the RT-PCR assays for the *E* gene, *RdRP* gene, and *N* gene (nucleocapsid protein) were performed with the Allplex 2019-nCoV Assay (Seegene Inc., Seoul, South Korea) in a Bio-Rad CFX96 Deep Well real-time PCR detection system (Bio-Rad, Hercules, CA, USA), after viral RNA extraction using a MagNA Pure 96 DNA and Viral NA Small Volume Kit (Roche Molecular Biochemicals, Indianapolis, IN, USA) in conjunction with the MagNa Pure 96 System (Roche Molecular Biochemicals) at Seegene Medical Foundation. The cutoff values for the RT-PCR assays were defined as Ct values of 33.5, 33.5, and 34.5 for the *E*, *RdRP*, and *N* gene, respectively (Hong et al., 2020).

Negative conversion was defined as two consecutive negative RT-PCR assay results within a 24-h interval. Patients with negative conversion were released from quarantine and discharged. The time until negative conversion was defined as the interval between diagnosis and the first RT-PCR-negative result at negative conversion. Rebound of the Ct value was defined as negative from the single RT-PCR assay and positive from the following RT-PCR assay.

The following were compared between the asymptomatic and symptomatic groups: baseline characteristics, laboratory findings at admission, positive RT-PCR rate each week (defined as the number of patients with a positive result divided by the number of patients who underwent RT-PCR assay testing), time until negative conversion, and the first follow-up Ct values and minimum follow-up Ct values for the *E*, *RdRP*, and *N* genes, as well as the changes in Ct values.

Statistical analysis

Continuous data are expressed as the median value with interquartile range (IQR), while categorical data are presented as the number and percentage (%). The Mann–Whitney *U*-test for continuous data and Fisher's exact test for categorical data were used to compare the clinical parameters between the two groups, as all datasets were non-normally distributed. A p-value < 0.05 for a two-sided test was considered statistically significant. Data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 422 patients were screened (median age 45.0 years (IQR 26.0–55.0 years), 36.0% male). Among them, 70 patients (16.6%) were asymptomatic throughout the disease course. Twenty-two patients were excluded because they were referred to the high-level hospitals due to worsening of their condition. Four patients were excluded because their negative conversion was not confirmed. Therefore, a total of 396 consecutive patients were included in this study. Their median age was 42.5 years (IQR 25.0–55.0 years, range 5–82 years) and 35.6% were male; 289 patients were from the Korea Workers' Compensation and Welfare

Services Daegu Hospital and 107 patients were from the Chungju Medical Center. Among the 396 patients, 68 (17.2%) were assigned to the asymptomatic group and 328 (82.8%) to the symptomatic group. The baseline characteristics are shown in Table 1.

Pulse rate, body temperature, white blood cell count, and C-reactive protein levels were significantly higher in the symptomatic group than in the asymptomatic group. All patients with obesity, asthma, chronic obstructive pulmonary disease, and coronary artery disease had COVID-19-related symptoms and were therefore included in the symptomatic group. There was no significant difference in age, sex, body mass index, past histories, prior medications, blood pressure, respiration rate, hemoglobin, proportions of neutrophils and lymphocytes, platelet count, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine

Table 1
Baseline characteristics; continuous data are expressed as median values (interquartile range) and categorical data are presented as numbers (%).

	Asymptomatic group ($n = 68$)	Symptomatic group ($n = 328$)	p-Value
Age (years)	33.5 (23.8–56.3)	44.0 (26.0–55.0)	0.168
Sex			0.070
Male	31 (45.6)	110 (33.5)	
Female	37 (54.4)	218 (66.5)	
Body mass index (kg/m^2)	22.4 (20.5–24.8)	23.0 (20.7–24.8)	0.531
Overweight	15 (22.1)	72 (22.0)	>0.999
Obese	0 (0)	11 (3.4)	–[a]
Symptoms			
Cough	0 (0)	197 (60.1)	–[a]
Sputum	0 (0)	146 (44.5)	–[a]
Sore throat	0 (0)	109 (33.2)	–[a]
Rhinorrhea	0 (0)	108 (32.9)	–[a]
Headache	0 (0)	82 (25.0)	–[a]
Chest pain	0 (0)	36 (11.0)	–[a]
Fever/chills	0 (0)	56 (17.1)	–[a]
Myalgia	0 (0)	76 (23.2)	–[a]
Dyspnea	0 (0)	58 (17.7)	–[a]
Anosmia	0 (0)	5 (1.5)	–[a]
Ageusia	0 (0)	3 (0.9)	–[a]
Diarrhea	0 (0)	42 (12.8)	–[a]
Interval between symptom onset and diagnosis (days)	–	4.0 (2.0–9.0)	–
Past history	14 (20.6)	73 (22.3)	0.873
Asthma	0 (0)	10 (3.0)	–[a]
COPD	0 (0)	2 (0.6)	–[a]
Hypertension	11 (16.2)	36 (11.0)	0.222
Diabetes	3 (4.4)	15 (4.6)	>0.999
Coronary artery disease	0 (0)	2 (0.6)	–[a]
Dyslipidemia	1 (1.5)	7 (2.1)	>0.999
Prior medications			
ACEI/ARB	6 (8.8)	19 (5.8)	0.278
Calcium channel blocker	2 (2.9)	11 (3.4)	>0.999
Statin	2 (2.9)	11 (3.4)	>0.999
Biguanide	2 (2.9)	9 (2.7)	>0.999
Systolic BP (mmHg)	129.0 (118.5–135.0)	129.0 (119.0–139.0)	0.462
Diastolic BP (mmHg)	78.0 (72.0–83.5)	78.0 (70.0–85.0)	0.655
Pulse rate (/min)	80.0 (71.0–90.3)	85.0 (77.0–94.0)	0.008
Respiration rate (/min)	20.0 (19.0–20.0)	20.0 (20.0–20.0)	0.816
Body temperature (°C)	36.9 (36.9–37.1)	37.0 (36.7–37.4)	0.004
Body temperature ≥37.5 °C	0 (0)	71 (21.6)	–[a]
O_2 saturation (%)	97.0 (97.0–98.0)	97.0 (97.0–98.0)	0.989
Chest X-ray or CT findings			
Unilateral pneumonia	0 (0)	53 (16.2)	–[a]
Bilateral pneumonia	0 (0)	61 (18.6)	–[a]
Laboratory findings			
Hemoglobin (g/dl)	13.8 (13.4–15.2)	13.7 (12.8–14.9)	0.307
WBC count (/μl)	5195 (4458–5835)	5825 (4855–6905)	0.007
Neutrophil (%)	53.7 (48.3–60.9)	57.2 (49.6–63.5)	0.091
Lymphocyte (%)	34.2 (29.4–39.8)	31.9 (26.5–38.8)	0.106
Platelet count (/μl)	261 000 (243 000–309 000)	258 000 (220 000–306 000)	0.353
BUN (mg/dl)	12.0 (10.8–13.7)	11.9 (10.0–14.3)	0.889
Creatinine (mg/dl)	0.9 (0.7–1.0)	0.8 (0.7–0.9)	0.012
AST (U/L)	20.0 (16.8–23.0)	21.0 (17.0–28.0)	0.199
ALT (U/L)	19.5 (12.8–27.0)	20.0 (13.0–31.8)	0.788
LDH (IU/L)	214.0 (180.0–231.0)	213.0 (176.3–255.8)	0.616
CRP (mg/dl)	0.1 (0.1–0.1)	0.1 (0.1–0.2)	0.004
Antimicrobial therapy			
Lopinavir/ritonavir	0 (0)	93 (28.4)	–[a]
Hydroxychloroquine	0 (0)	39 (11.9)	–[a]
Third-generation cephalosporin	0 (0)	78 (23.8)	–[a]
Azithromycin	0 (0)	71 (21.6)	–[a]

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST; aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; WBC, white blood cell.

[a] Statistical comparison could not be performed because the number of patients was small.

Table 2
Data on follow-up RT-PCR assays for SARS-CoV-2; Continuous data are expressed as median values (interquartile range) and categorical data are presented as numbers (%).

	Asymptomatic group ($n = 68$)	Symptomatic group ($n = 328$)	p-Value
Interval between diagnosis and the first follow-up RT-PCR assay (days)	9.5 (7.0–14.0)	16.0 (13.0–19.0)	<0.001
Number of follow-up RT-PCR assays	3.0 (2.0–5.0)	2.0 (2.0–4.0)	0.055
Median interval between follow-up RT-PCR assays (days)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.430
Time until negative conversion (days)	14.5 (11.0–21.0)	18.0 (15.0–22.0)	0.001
Rebound of Ct value	15 (22.1)	63 (19.2)	0.616

Ct, cycle threshold; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

aminotransferase, or lactate dehydrogenase between the two groups. All patients in both groups were discharged from the hospital without any sequelae.

Data on the follow-up RT-PCR assays for SARS-CoV-2 are shown in Table 2. The interval between diagnosis and the first follow-up RT-PCR assay was significantly shorter in the asymptomatic group than in the symptomatic group. There was no significant difference in the number of follow-up RT-PCR assays or median interval between follow-up RT-PCR assays between the two groups. The time until negative conversion was significantly shorter in the asymptomatic group than in the symptomatic group: median 14.5 days (IQR 11.0–21.0 days, range 6.0–40.0 days) and median 18.0 days (IQR 15.0–22.0 days, range 4.0–46.0 days), respectively ($p = 0.001$).

The proportion of patients with negative conversion according to the time until negative conversion in the asymptomatic and symptomatic groups is shown in Figure 1. In the asymptomatic group, negative conversion was achieved within 1 week in 11.8%, 2 weeks in 50.0%, 3 weeks in 76.5%, 4 weeks in 92.6%, and 5 weeks in 98.5% of the patients. In the asymptomatic group, negative conversion was not achieved within 30 days in 5.9% of the patients. In contrast, in the symptomatic group, negative conversion was achieved within 1 week in 2.7%, 2 weeks in 21.6%, 3 weeks in 74.1%, 4 weeks in 89.9%, and 5 weeks in 97.9% of the patients. In the symptomatic group, negative conversion was not achieved within 30 days in 6.7% of the patients.

Changes in the proportion of patients without negative conversion according to hospitalization day are shown in Figure 2. The proportion of patients with negative conversion within 20 days was significantly higher in the asymptomatic group than in the symptomatic group, while the proportion of patients with negative conversion in 20 days was similar in the two groups. There was no significant difference in the positive RT-PCR rate between the groups on days 7, 14, 21, and 28 since diagnosis among the patients who underwent follow-up RT-PCR assays (Table 3).

RT-PCR assays for the *E* and *RdRP* genes were performed for all patients, while the RT-PCR assay for the *N* gene was performed for 107 patients. There was no significant difference in the first follow-up Ct value for the *E*, *RdRP*, and *N* genes between the two groups (Supplementary Material Table S1). There was no significant difference in minimum follow-up Ct value of the *E*, *RdRP*, and *N* genes between the two groups (Supplementary Material Table S1). There was no significant difference in rebound of Ct values between the two groups (Table 2). Serial changes in Ct values for the three genes in the asymptomatic and symptomatic groups are shown in Figure 3.

Discussion

Main findings of this study

The main findings of this retrospective cohort study were as follows: (1) approximately 17% of the patients with COVID-19 exhibited no symptoms; (2) all of the patients with obesity, asthma, chronic obstructive pulmonary disease, and coronary artery disease had COVID-19-related symptoms; (3) the median time from diagnosis to negative conversion was approximately 2 weeks in the natural course of asymptomatic COVID-19–that is, negative conversion was not achieved 2 weeks after diagnosis in approximately half of the asymptomatic patients with COVID-19; (4) time until negative conversion was shorter in asymptomatic COVID-19 than in symptomatic COVID-19; (5) rebound of Ct values was not uncommon in follow-up RT-PCR assays; and (6) there was no significant difference in rebound of Ct values between the asymptomatic and symptomatic patients.

Prior studies on asymptomatic COVID-19

Given that asymptomatic cases are known to play a role in disease transmission (Bai et al., 2020; Pan et al., 2020a, b; Rothe

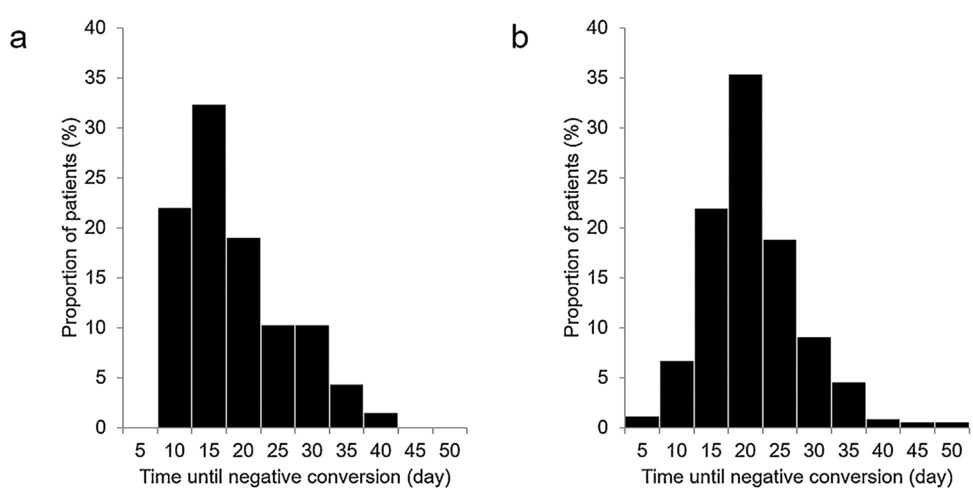
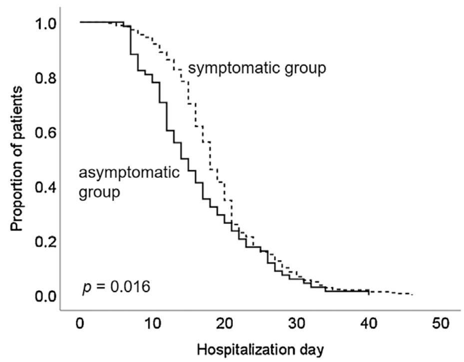


Figure 1. The proportion of patients with negative conversion according to time until negative conversion in the asymptomatic (A) and symptomatic (B) groups.



Number at risk

Asymptomatic group	68	53	18	4	0	0
Symptomatic group	328	302	114	22	4	0

Figure 2. Changes in the proportion of patients without negative conversion relative to hospitalization day.

et al., 2020; Ye et al., 2020), it is essential to know the proportion of such cases relative to symptomatic cases and the characteristics of viral shedding in asymptomatic infection to establish guidelines for the management of COVID-19. The proportion of asymptomatic infection has been estimated to be 17.9–30.8% (Mizumoto et al., 2020; Nishiura et al., 2020).

If patients have no symptoms at the time of diagnosis, it is difficult to distinguish persistently asymptomatic patients throughout the disease course from patients in the presymptomatic period. According to a report on 13 asymptomatic patients with COVID-19, 12 patients had radiological abnormalities and three patients developed symptoms (Zhou et al., 2020). Approximately 9.6% of residents in Wuhan, China who had never been symptomatic yet were diagnosed with COVID-19 exhibited positive IgG-antibody test results for SARS-CoV-2, suggesting that they had had an asymptomatic infection (Wu et al., 2020). The results of the present study are consistent with prior findings that the Ct values in asymptomatic patients are not significantly different from those in symptomatic patients (Zou et al., 2020).

A previous study demonstrated that the time from diagnosis to negative conversion was 7.5 days in persistently asymptomatic patients with normal or atypical chest CT findings and 12.5 days in persistently asymptomatic patients with pneumonia (Pan et al., 2020a, b). There was a difference in the time until negative conversion between this previous study and the present study. This might be because the interval from disease onset to diagnosis was longer in the previous study than in the present study. Another previous study showed that asymptomatic patients had a longer duration of viral shedding than symptomatic patients, in contrast to the present study (Long et al., 2020). It has been suggested that asymptomatic cases show relatively smaller transmission rates than symptomatic cases (He et al., 2020).

Differences in baseline characteristics between the groups

In Daegu, South Korea, mass investigation and mass testing, as well as active surveillance, have been performed throughout the COVID-19 outbreak. As a result, a number of asymptomatic patients with COVID-19 were detected. Among the population in this study, 95.5% of the patients were residents of Daegu. While hospital beds were limited, some asymptomatic or mildly symptomatic patients with COVID-19 were quarantined at home or in dedicated COVID-19 facilities. Therefore, the proportion of asymptomatic patients in this study might be underestimated.

In the present study, all COVID-19 patients with obesity, asthma, chronic obstructive pulmonary disease, and coronary artery disease had symptoms. This might be because they are susceptible to the development of COVID-19-related symptoms or because symptoms related to these underlying diseases might be confused with COVID-19-related symptoms. In the symptomatic patients, body temperature, white blood cell count, and the C-reactive protein level were higher than in the asymptomatic patients. These findings suggest that symptomatic patients might mount a stronger inflammatory reaction than asymptomatic patients. A high pulse rate may be associated with a high body temperature in symptomatic patients.

Clinical implications of this study

Although it was unclear when exposure to SARS-CoV-2 may have occurred, the median duration of disease in asymptomatic COVID-19 must be longer than 14.5 days. The reasons for the shorter time until negative conversion in the asymptomatic patients might have been because of a short disease duration or delayed diagnosis. The optimal time at which the first follow-up RT-PCR assays should be performed in asymptomatic patients can be decided based on the present study results. Rebound of Ct values was observed in a considerable number of patients. Although the reasons for rebound of Ct values remain unclear, possible explanations include reactivation of SARS-CoV-2, inadequate specimen collection, and laboratory errors. In any case, negative results for two consecutive RT-PCR assays within a 24-h interval can be considered a reasonable criterion for lifting the quarantine.

No studies have yet dealt with the clinical characteristics and viral kinetics of a larger number of asymptomatic patients, and studies reporting comparisons of the characteristics and changes in RT-PCR results in asymptomatic patients with those in symptomatic patients are also scarce. The results of the present study provide the rationale for a quarantine strategy for asymptomatic people who have been exposed to patients with COVID-19, including recommendations on when best to perform follow-up RT-PCR assays for asymptomatic patients with COVID-19 in the midst of shortages of medical facilities and equipment during the COVID-19 outbreak.

Table 3
Positive RT-PCR rates at each week among the patients who underwent follow-up RT-PCR assays; positive RT-PCR rates are expressed as (the number of patients with positive results)/(the number of patients who underwent RT-PCR assay) and the percentage (%).

Positive RT-PCR rate on the following days since diagnosis:	Asymptomatic group ($n = 68$)	Symptomatic group ($n = 328$)	p-value
Day 7	14/22 (63.6)	15/24 (62.5)	0.936
Day 14	19/53 (35.8)	54/125 (43.2)	0.362
Day 21	13/65 (20.0)	57/300 (19.0)	0.853
Day 28	4/67 (6.0)	27/322 (8.4)	0.507

RT-PCR, reverse transcriptase polymerase chain reaction.

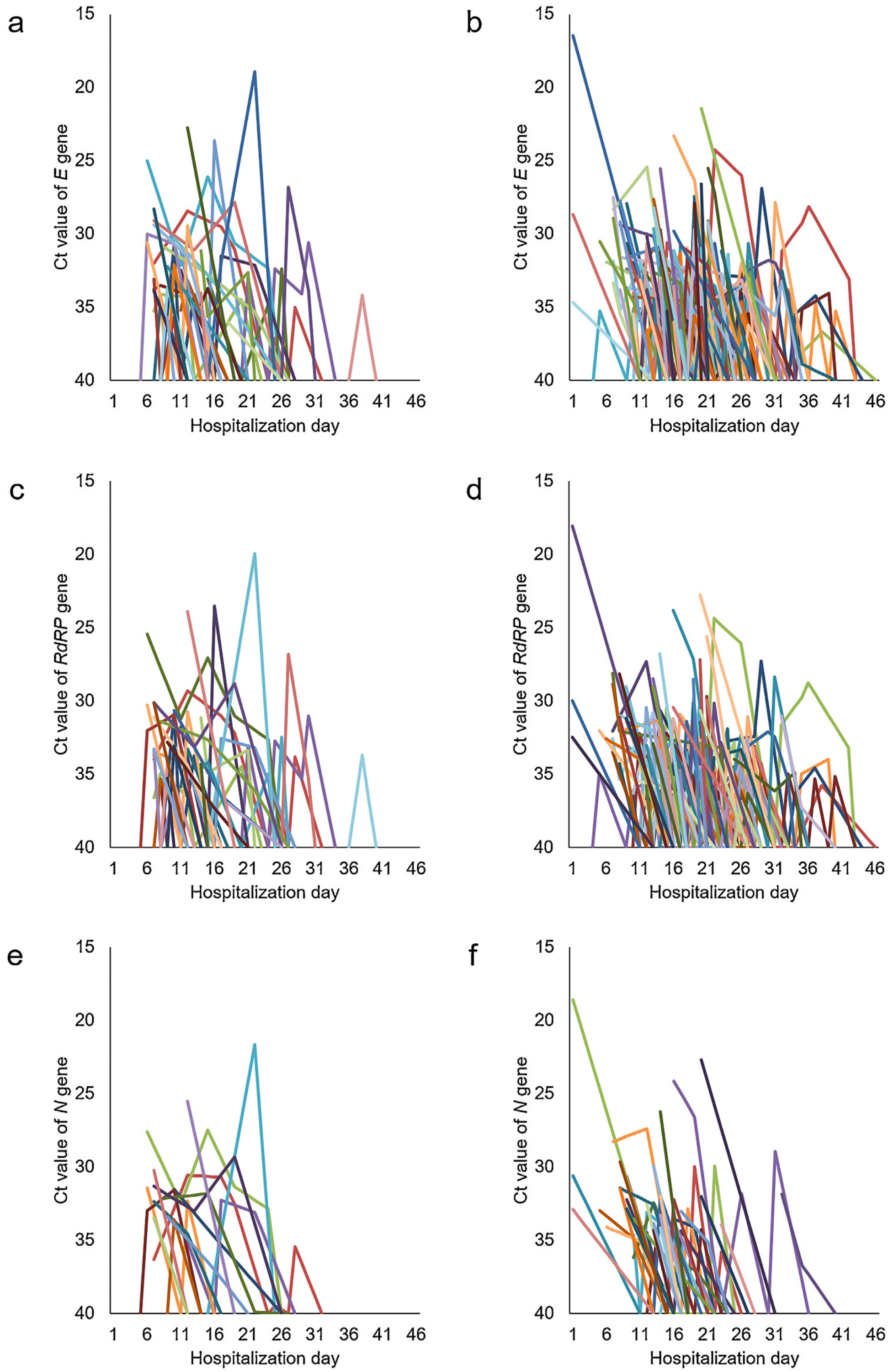


Figure 3. Changes in Ct value from RT-PCR assays for the *E* gene of SARS-CoV-2 in the asymptomatic (A) and symptomatic (B) groups, *RdRP* gene of SARS-CoV-2 in the asymptomatic (C) and symptomatic (D) groups, and *N* gene[a] of SARS-CoV-2 in the asymptomatic (E) and symptomatic (F) groups. Each line represents one patient.
[a]The RT-PCR assay for the *N* gene was performed in 23 patients in the asymptomatic group and 84 patients in the symptomatic group.
Ct, cycle threshold; E, envelop protein; N, nucleocapsid protein; RdRP, RNA-dependent RNA polymerase; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Limitations and strengths of this study

This study had several limitations. First, the time of exposure to SARS-CoV-2 was unclear for a number of patients. Therefore, it was difficult to specify the onset of the disease in asymptomatic patients. Second, only nasopharyngeal specimens were collected from all patients. RT-PCR positivity can be higher or more prolonged for lower respiratory specimens (Sethuraman et al., 2020; Wang et al., 2020). Third, the Ct values at diagnosis were unavailable. Fourth, given that the present study was retrospective, the follow-up intervals of RT-PCR assays lacked uniformity and density. In particular, the intervals between diagnosis and the first follow-up RT-PCR assay differed between the asymptomatic and symptomatic groups because existing recommendations on when to perform the first follow-up RT-PCR assay were different in the two groups. Fifth, the RT-PCR assay for the *N* gene was not performed in all patients. Sixth, Ct values may not be linearly correlated to viral load. Seventh, chest CT was not performed in all patients. Specifically, the patients with normal chest X-ray results did not undergo chest CT.

Despite these limitations, this study had several strengths. A significant number of asymptomatic patients were included. Serial RT-PCR results were analyzed throughout the disease course. These findings may contribute to establishing guidelines for the management of asymptomatic COVID-19 in pandemic situations and shortages of medical resources.

Conclusions

Time until negative conversion is shorter in asymptomatic COVID-19 than in symptomatic COVID-19. Rebound of Ct values is not uncommon.

Author contributions

Concept and design of the study: J.-S.U., J.Y.A., J.-S.Y., and Y.S.P. Acquisition of the data: J.H.H., Y.S., J.H.K., S.J.J., N.S.K., J.Y.C., Y.-K.P., H.Y., S.K.P., B.-O.K., H.K., J.C., S.K., Y.H.C., H.K.Y., S.J., and H.N.K. Data analysis and interpretation of the data: J.-S.U., J.Y.A., J.-S.Y., and Y.S. P. Drafting the manuscript: J.-S.U. and J.Y.A. Critical revision of the manuscript: J.H.H., Y.S., J.H.K., S.J.J., N.S.K., J.Y.C., Y.-K.P., H.Y., S.K.P., B.-O.K., H.K., J.C., S.K., Y.H.C., H.K.Y., S.J., H.N.K., J.-S.Y., and Y.S.P. All authors approved the final version of the manuscript.

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Ethical approval

The study design was approved by the Institutional Review Board (IRB number 4-2020-0329 and 9-2020-0020) and the study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board waived both the need for the acquisition of informed consent from patients to be included in the analysis and the need for review by a critical event committee, owing to the retrospective nature of the study and the absence of patient identification in the data presented.

Conflict of interest

S. Jung is an employee of Seegene Medical Foundation. H.N. Kim is an employee of Samkwang Medical Laboratories.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.07.070.

References

Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020;323:1406–7.
Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
Choi WS, Kim HS, Kim B, et al. Community treatment centers for isolation of asymptomatic and midly symptomatic patients with coronavirus disease, South Korea. Emerg Infect Dis 2020;26:, doi:http://dx.doi.org/10.3201/eid2610.201539.
He D, Zhao S, Lin Q, et al. The relative transmissibility of asymptomatic COVID-19 infections among close contacts. Int J Infect Dis 2020;94:145–7.
Hong KH, Lee SW, Kim TS, et al. Guidelines for laboratory diagnosis of coronavirus disease 2019 (COVID-19) in Korea. Ann Lab Med 2020;40:351–60.
Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020;, doi:http://dx.doi.org/10.1038/s41591-020-0965-6.
Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74.
Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200:e45–67.
Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill 2020;25:2000180.
Nishiura H, Kobayashi T, Suzuki A, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis 2020;94:154–5.
Pan X, Chen D, Xia Y, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. Lancet Infect Dis 2020a;20:410–1.
Pan Y, Yu X, Du X, et al. Epidemiological and clinical characteristics of 26 asymptomatic SARS-CoV-2 carriers. J Infect Dis 2020b;221:1940–7.
Park PG, Kim CH, Heo Y, et al. Out-of-hospital cohort treatment of coronavirus disease 2019 patients with mild symptoms in Korea: an experience from a single community treatment center. J Korean Med Sci 2020;35:e140.
Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020;382:970–1.
Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020;, doi:http://dx.doi.org/10.1001/jama.2020.8259.
Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323:1843–4.
Wu X, Fu B, Chen L, Feng Y. Serological tests facilitate identification of asymptomatic SARS-CoV-2 infection in Wuhan, China. J Med Virol 2020;, doi:http://dx.doi.org/10.1002/jmv.25904.
Ye F, Xu S, Rong Z, et al. Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster. Int J Infect Dis 2020;94:133–8.
Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. Clin Microbiol Infect 2020;26:957–9.
Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382:1177–9.