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Coronavirus Pandemic

Factors associated with prolonged viral detection in asymptomatic and mildly symptomatic patients with SARS-CoV-2 infection

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Abstract

Introduction: Data on the clinical course and duration of viral RNA detection in patients with mild or asymptomatic coronavirus disease 2019 are limited.

Methodology: In this retrospective analysis, clinical characteristics and serial real-time reverse transcriptase-polymerase chain reaction (RT-PCR) results were reviewed in a cohort of 1186 asymptomatic and mildly symptomatic coronavirus disease 2019 patients in South Korea. Factors associated with prolonged duration of RT-PCR positivity for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) were also evaluated. Patients with two consecutive negative RT-PCR tests ≥ 24 hours apart were considered to be in virologic remission and discharged.

Results: The average virologic remission period, defined as the number of days from diagnosis to virologic remission, was 22.0 ± 9.7 days; patients with longer than 30 days accounted for 21.2% (251/1186) of the population. Patients who took longer than 30 days to achieve virologic remission had a higher frequency of overall symptoms ($p < 0.001$) and respiratory symptoms ($p < 0.001$). In multivariate analysis using Cox-proportional hazard regression, it was confirmed that respiratory symptoms (hazard ratio [HR], 0.7372; 95% confidence interval [CI], 0.6540-0.8311) and gastrointestinal symptoms (HR, 0.8213; 95% CI, 0.6970-0.9679) were independent factors associated with prolonged virologic remission. Age and co-morbidity such as diabetes and hypertension were not associated with the prolonged RT-PCR positivity.

Conclusions: A considerable percentage of asymptomatic and mildly symptomatic patients with coronavirus disease 2019 showed prolonged RT-PCR positivity for SARS-CoV-2; which was independently associated with the presence of symptoms, but not with age and co-morbidity.

Key words: SARS-CoV-2; COVID-19; Community Treatment Center; RT-PCR; Symptoms; Comorbidity.

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Introduction

The coronavirus disease 2019 (COVID-19) has continued to spread throughout the globe since it was declared a pandemic in March 2020 [1]. As of November 2020, the number of confirmed cases has exceeded 50 million worldwide, and more than 1.3 million people have died [2]. Along with this severe health impact, the pandemic has created a socio-economic crisis leaving countries struggling to overcome the disease's devastating effects [3].

While the largest proportion of cases are mild, the clinical spectrum of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) can vary from asymptomatic to the most serious conditions that lead to hospitalization and death [4,5]. The proportion of those infected with COVID-19 who are undiagnosed or have minimal symptoms, but can still actively transmit the disease, propels the expansion of the pandemic [6]. Therefore, it is crucial to properly isolate and monitor the asymptomatic and mildly symptomatic patients.

Given these circumstances, Korea created temporary community treatment centers (CTCs) in March 2020 to isolate asymptomatic to mildly symptomatic patients who do not need to be hospitalized; this allowed the limited availability of advanced medical resources to be reserved for the more severely ill patients [7].

Several studies have been published on the clinical characteristics of asymptomatic or mildly symptomatic patients [8-12], but data are still lacking about the viral detection and clinical course of mild or asymptomatic COVID-19 patients. This study describes the disease

course of patients admitted to four CTCs and identifies factors associated with prolonged duration of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) positivity for SARS-CoV-2.

Methodology

Study design and participants

We retrospectively identified 1242 asymptomatic and mildly symptomatic patients who had tested positive for SARS-CoV-2 by RT-PCR and had been admitted to one of three CTCs or a regional center hospital dedicated for COVID-19 in the Daegu-Gyeongbuk providence of South Korea between Feb 21 to Apr 29, 2020: Daegu 1 CTC, Daegu 2 CTC, Gyeongbuk-Daegu 7, and Daegu Dongsan hospital. Initially, every patient diagnosed as COVID-19 was admitted to the regional center hospital dedicated for COVID-19. Because of rapid surge of COVID-19 in our region, asymptomatic and mildly symptomatic patients were admitted at CTCs after March 2, 2020.

During our study period the Korean Centers for Disease Control and Prevention (KCDC) suggested patient classification guideline: asymptomatic, mild, severe and very severe [13]. The patients classified as asymptomatic or mildly symptomatic were eligible for this study. Severe patients were defined as persons who were alert but had dyspnea or temperature ≥ 38 °C despite taking antipyretic drugs, and very severe patients were persons who had decreased alertness. Severe or very severe, and high-risk (persons ≥ 65 years of age, those with oxygen saturation < 90% on room air, or those with notable chronic underlying diseases) patients were admitted to hospitals. However, some high-risk asymptomatic and mildly symptomatic patients were admitted at our CTCs due to the rapid surge of the patients and hospital overload. If one CTC closed, its patients were transferred to one of the remaining CTCs. Patients were excluded from our analysis if they were transferred to the hospital due to worsening of disease (n = 30) or to other CTCs (n = 26). The institutional review board of Kyungpook National University Hospital approved this study design, and informed consent was waived (IRB no. 2020-04-052).

As described in earlier studies [8,14], the CTCs were existing facilities that were temporarily converted to isolate and monitor COVID-19-confirmed patients. The patients were assessed by telephone interview twice a day. The patients routinely self-monitored and reported their symptoms and temperatures, and they could request an in-room examination by medical staff. Chest radiography and oxygen saturation measurements were performed at the physicians' discretion. Conservative treatment, such as antipyretics, was provided for mild symptoms, but patients who needed advanced medical care were transferred to the hospital.

Laboratory test and discharge criteria

To conduct RT-PCR testing, patients' nasopharyngeal and oropharyngeal swab specimens were collected by physicians and sent to the core laboratory facility in the tertiary hospital. The results were interpreted by a medical laboratory specialist. Patients were given an RT-PCR test five to seven days after admission, if there were no further aggravation of the symptom; a second test was given 24 hours after a negative test, three to seven days after a positive test, or two days after an inconclusive test. In compliance with KCDC guidelines [13], patients with two consecutive negative RT-PCR tests ≥ 24 hours apart were considered to be in virologic remission and discharged.

Data collection

We retrospectively collected data on patients from the admission date until discharge. Data on patients' age and gender, comorbid conditions, symptoms, and RT-PCR results were reviewed from the electronic medical record. Respiratory symptoms were defined as dyspnea, cough, sputum, rhinorrhea, or sore throat; gastrointestinal symptoms were diarrhea, dyspepsia, or constipation.

Statistical analysis

We analyzed the data using R version 4.0.3 software (https://www.r-project.org) and considered $p < 0.05$ to be statistically significant. We noted continuous and categorical variables as mean ± standard deviation and number (%). We defined the virologic remission period as the number of days from diagnosis to virologic remission. Chi-square tests were used for categorical variables, and t-tests were used for continuous variables. One-way ANOVA was used for comparing continuous variables in three groups. We performed a Cox-proportional hazard regression to evaluate each factor related to virologic remission period, such as age, sex, underlying conditions, and symptoms. Multivariate analysis was also performed using Cox-proportional hazard regression, and variables with p values < 0.3 on univariate analysis are included in the model: age, dyslipidemia, fever, respiratory symptoms, gastrointestinal symptoms, and other symptoms. Hazard ratio (HR) with 95% confidence interval (CI) was provided for the model.

For further analysis of the classification and regression tree (CART), input variables were variables $p < 0.3$ in univariate analysis of Cox-proportional hazard regression. These factors were analyzed together using "ctree" of the "party" package. The tree chart was generated with the input data of the variables and virologic remission period.

Results

Patient characteristics

One thousand one hundred and eighty-six patients were enrolled in this study. There were 403 (34.0%) males and 783 (66.0%) females; the mean age was 40.0 years (SD ± 16.1), and 219 patients (18.5%) had ≥ 1 underlying condition. Five hundred forty-six (46.0%) patients had no symptoms throughout the illness period. Among the 640 (54.0%) symptomatic patients, 543 (45.8%) had respiratory symptoms, followed by 172 (14.5%) patients with gastrointestinal symptoms (Table 1). The average virologic remission period for all study populations was 22.0 ± 9.7 days, and patients with positive results for more than 30 days accounted for 21.2% (n = 251).

Comparison of clinical characteristics

The clinical characteristics of the study patients were compared by dividing the period from diagnosis to discharge (confirmation of negative results) into two groups: prolonged positivity group (more than 30 days), and early conversion group (less than 30 days) (Table 1). No significant differences were found between the two groups in age, gender, or comorbid conditions. The presence of symptoms was significantly more common in the prolonged positivity group than in the early conversion group (165 [65.7%] vs. 475 [50.8%], $p < 0.001$). The frequency of respiratory symptoms was higher in the prolonged positivity group (144 [57.4%] vs. 399 [42.7%], $p < 0.001$).

Univariate and multivariate analysis according to the virologic remission period

Univariate analysis was performed using the Cox-proportional hazard regression. Significant prognostic factors by univariate analysis were the presence of any symptom (HR, 0.6830; 95% CI, 0.6091-0.7659; $p < 0.001$), fever (HR, 0.7626; 95% CI, 0.5959–0.9760; $p = 0.031$), respiratory symptoms (HR, 0.7162; 95% CI, 0.6387–0.8031; $p < 0.001$), gastrointestinal symptoms (HR, 0.7707; 95% CI, 0.6556–0.9060; $p = 0.002$), and other symptom (HR, 0.8330; 95% CI, 0.7056–0.9834; $p = 0.031$).

Multivariate analysis was conducted to find independent factors. Table 2 shows significant factors: presence of respiratory symptoms (HR, 0.7372; 95% CI, 0.6540–0.8311; $p < 0.001$) and gastrointestinal symptoms (HR, 0.8213; 95% CI, 0.6970–0.9679; $p =$

Table 1. Patient characteristics.

	Overall	Remission period		
	N = 1186	< 30 N = 935	≥ 30 N = 251	*p* value
Gender				**0.740**
Male	403 (34.0%)	315 (33.7%)	88 (35.1%)	
Female	783 (66.0%)	620 (66.3%)	163 (64.9%)	
Age				**0.157**
Mean ± SD	40.0 ± 16.1	40.3 ± 16.4	38.8 ± 15.0	
< 50	756 (63.7%)	587 (62.8%)	169 (67.3%)	
≥ 50	430 (36.3%)	348 (37.2%)	82 (32.7%)	
Comorbidity				
None	967 (81.5%)	763 (81.6%)	204 (81.3%)	
Any comorbidity	219 (18.5%)	172 (18.4%)	47 (18.7%)	0.978
Hypertension	89 (7.5%)	70 (7.5%)	19 (7.6%)	> 0.999
Diabetes	28 (2.4%)	19 (2.0%)	9 (3.6%)	0.228
Dyslipidemia	32 (2.7%)	28 (3.0%)	4 (1.6%)	0.319
Respiratory disease	31 (2.6%)	27 (2.9%)	4 (1.6%)	0.359
Other	91 (7.7%)	71 (7.6%)	20 (8.0%)	0.949
Symptom				
None	546 (46.0%)	460 (49.2%)	86 (34.3%)	
Any symptoms	640 (54.0%)	475 (50.8%)	165 (65.7%)	< 0.001
Fever	67 (5.6%)	47 (5.0%)	20 (8.0%)	0.101
Respiratory	543 (45.8%)	399 (42.7%)	144 (57.4%)	< 0.001
Gastrointestinal	172 (14.5%)	126 (13.5%)	46 (18.3%)	0.066
Headache	104 (8.8%)	80 (8.6%)	24 (9.6%)	0.708
Other	162 (13.7%)	123 (13.2%)	39 (15.5%)	0.383

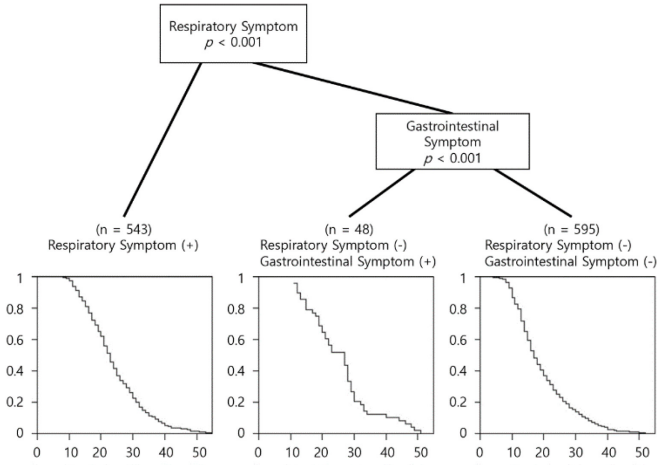
0.019). In CART analysis, respiratory symptom was most the powerful prognostic factor and gastrointestinal symptoms were also a significant prognostic factor (Figure 1). Virologic remission period of patients with respiratory symptom was 24.10 ± 9.4 days, that of no respiratory symptom and positive gastrointestinal symptom was 25.6 ± 10.4 days, and no respiratory symptom and no gastrointestinal symptom was 19.8 ± 9.3 days.

Discussion

The present study was conducted to identify factors associated with prolonged RT-PCR positivity for SARS-CoV-2 in asymptomatic and mildly symptomatic COVID-19 patients; we classified patients based on their length of stay; 21% of the 1186 study patients required more than 30 days to achieve a negative viral RNA test. While the presence of symptoms (especially respiratory symptoms) was identified as an independent factor related to prolonged RT-PCR positivity, there was no significant association with age and underlying diseases.

Our study population was relatively young, with an average age of 40 years and included a higher proportion of women. These demographic characteristics were similar to recently reported studies of patients admitted to other CTCs in Korea; mass infection through exposure at a Daegu religious facility prompted several CTCs to begin operations in March 2020 [7,10,15]. The average interval from diagnosis to discharge in previous CTC studies was reported to be about 20 days [9,10], similar to our study.

Figure 1. Results of Classification and regression tree (CART).



CART analysis was performed to verify the prognostic factors of prolonged duration of RT-PCR positivity. Square boxes indicate subsets of patients defined by the sequential-splitting process. Respiratory symptom was the most powerful prognostic factor, and the gastrointestinal symptoms were identified as significant prognostic factors in patients without respiratory symptom.

Twenty-three percent of patients in our study were found to be RT-PCR positive for 30 days or more. A study of CTCs in Seoul showed that 30% of patients who were discharged to home after recovering had stayed in a CTC for over four weeks [11]; with our findings, this suggests that viral RNA could be detected for 30 days or longer in a significant proportion of COVID-19 patients with mild or no symptoms.

In our previous study which analyzed patient data recruited from two CTCs, also included in the current

Table 2. Univariate and multivariate analysis of virologic remission period.

	Univariate analysis			Multivariate analysis		
	Hazard Ratio	**95% CI**	***p* value**	**Hazard Ratio**	**95% CI**	***p* value**
Age	1.0021	0.9985-1.0060	0.257	1.0035	0.9998 - 1.0073	0.065
Sex						
Male	0.9559	0.8472-1.0790	0.464			
Comorbidity						
Any comorbidity	0.9896	0.8545-1.1460	0.889			
Hypertension	1.0113	0.8147-1.2550	0.919			
Diabetes	0.8576	0.5894-1.2480	0.422			
Dyslipidemia	1.2843	0.9032-1.8260	0.164	1.3932	0.9672 - 2.0068	0.075
Respiratory disease	1.1734	0.8210-1.6770	0.380			
Other	0.9452	0.7632-1.1710	0.606			
Symptom						
Any symptom	0.6830	0.6091-0.7659	< 0.001			
Fever	0.7626	0.5959-0.9760	0.031	0.8332	0.6410 - 1.0830	0.173
Respiratory	0.7162	0.6387-0.8031	< 0.001	0.7372	0.6540 - 0.8311	< 0.001
Gastrointestinal	0.7707	0.6556-0.9060	0.002	0.8213	0.6970 - 0.9679	0.019
Headache	0.9137	0.7468-1.1180	0.380			
Other	0.8330	0.7056-0.9834	0.031	0.9416	0.7909 - 1.1209	0.499

Multivariate analysis was performed with the variables with *p* values < 0.3 on univariate analysis: age, dyslipidemia, fever, respiratory symptoms, gastrointestinal symptoms, and other symptoms.

study, the duration of RT-PCR positivity of symptomatic patients was significantly longer than that of asymptomatic patients [8], whereas another study of CTCs showed that the presence or absence of clinical symptoms did not predict persistent detection of virus ≥ 28 days [9]. Our current study with a larger number of patients affirmed our earlier finding that the presence of symptoms was independently associated with prolonged RT-PCR positive test results. In addition, our results reflect a different study on the viral dynamics of patients hospitalized with COVID-19 [16]. In analyzing the cycle threshold (CT) values of serial nasopharyngeal swab samples, the viral load was found to be higher in patients with severe COVID-19 symptoms than in those having mild cases; patients with more symptoms had positive RT-PCR results for a longer period of time [16]. In CART analysis of our study, respiratory symptom was the most powerful prognostic factor associated with prolonged viral RNA detection; gastrointestinal symptoms could also predict prolonged RT-PCR positivity in patients without respiratory symptoms. Although SARS-CoV-2 is primarily known to invade the respiratory system, gastrointestinal symptoms are common; intestinal tropism and viral shedding in feces have been noted [17,18].

We found that symptomatic patients had relatively longer virologic remission period, but do not seem to always have a higher viral load. A previous study that included patients with COVID-19 isolated in a CTC in Korea demonstrated that the CT values of RT-PCR for SARS-CoV-2 in asymptomatic patients were similar to those in symptomatic patients [19]. Several other studies also reported there was no significant difference in viral load depending on whether accompanying symptoms were present [20-22]. Further research is needed to better understand the overall viral dynamics of the disease course between symptomatic and asymptomatic patients with COVID-19.

It is worth noting that age or underlying diseases did not have a significant relationship with prolonged RT-PCR positivity in our study patients, which is consistent with the previous study of other CTCs [9]. In a study of COVID-19 inpatients, it was reported that older patients showed greater severity and longer disease course [23]. Comorbid conditions such as hypertension and diabetes have also been suggested as predictors of adverse outcomes of patients with COVID-19 [24,25]. This is in line with the results of our earlier study of CTCs, which confirmed the association of age and underlying conditions with transfer to hospital [8]. However, the current study results suggest that the importance of such demographic characteristics may not be significant in terms of the duration of disease, which is one of the main treatment outcomes in the group of mild COVID-19 patients recovering without hospital transfer. Even though our study population was predominantly women and relatively young, age and underlying disease did not have relationship with virologic remission period in univariate and multivariate analysis. These demographic findings could be characteristics of asymptomatic or mildly symptomatic patients of COVID-19. Although the results of our study cannot be applied to all patients with COVID-19 of varying severity, they are likely to be helpful at least for operating facilities such as CTC or following self-isolated patients. When screening patients who are expected to be positive for PCR for a relatively longer duration, it seems necessary to focus on the occurrence of symptoms rather than age or comorbid conditions.

The clinical significance of prolonged RT-PCR positivity for SARS-CoV-2, major concern of our study, is not clear. Detection of viral RNA does not necessarily mean that the virus is viable or transmissible [26]. There are recent studies reporting that no live virus was cultured from patients' respiratory samples approximately one week after the onset of symptoms [27,28]. In a study that analyzed negative-to-positive RT-PCR test reversals, no infective viral strain could be isolated, and no full-length viral genomes could be sequenced [29]. To reduce the usage of limited hospital and testing resources, it has recently been suggested that patients should be released from isolation based on analysis of symptoms rather than testing results. However, symptom-based criteria do not eliminate the possibility of transmission to the community. In situations where even a minimal residual risk of transmission is not acceptable, test-based criteria may still be recommended [26]. Viral diagnostic testing still plays a conditional role in the latest recommendations to release patients from quarantine [26,30,31]; as of November 2020, tests are still being used as part of the release criteria in Korea [32]. In addition, during the 2003 SARS epidemic, disease transmission by close contact with patients discharged on a non-test basis has been suggested [33]. Until better data are available about virus shedding over the natural course of COVID-19, patients with prolonged RT-PCR positivity may need to be monitored closely and strictly should follow isolation guidelines of good personal hygiene and mask-wearing.

This study has several limitations. There may be some information missing from our analysis due to the limited number of medical staff and the risk of virus

transmission during pandemic situation, even though we tried to do our best in this limited circumstance. It was impossible to devote sufficient time to interview patients about their symptoms and underlying medical conditions completely. Therefore, some symptoms (such as loss of smell or taste) were not properly documented. RT-PCR tests were performed using only specimens from the respiratory tract. It has been reported that SARS-CoV-2 RNA could also be detected in serum, urine, or stool samples [34]. The data on additional viral load such as cycle threshold values were not obtained from the RT-PCR test results. Future large-scale studies using various samples and respiratory swabs are needed.

Conclusions

In conclusion, a considerable proportion of asymptomatic and mildly symptomatic patients with COVID-19 showed prolonged RT-PCR positivity for SARS-CoV-2. The strongest independent predictive indicator was the presence of respiratory symptoms, whereas age and underlying conditions were not significant. Further studies are needed to clarify the risks of infection transmission from COVID-19 patients who have prolonged RT-PCR positivity.

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Authors' Contributions

Yong Hoon Lee and Chae Moon Hong contributed equally to this article

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