

Original Article



Characteristics and Prevalence of Sequelae after COVID-19: A Longitudinal Cohort Study

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ABSTRACT

Background: The World Health Organization has declared the end of the coronavirus disease 2019 (COVID-19) public health emergency. However, this did not indicate the end of COVID-19. Several months after the infection, numerous patients complain of respiratory or nonspecific symptoms; this condition is called long COVID. Even patients with mild COVID-19 can experience long COVID, thus the burden of long COVID remains considerable. Therefore, we conducted this study to comprehensively analyze the effects of long COVID using multi-faceted assessments.

Materials and Methods: We conducted a prospective cohort study involving patients diagnosed with COVID-19 between February 2020 and September 2021 in six tertiary hospitals in Korea. Patients were followed up at 1, 3, 6, 12, 18, and 24 months after discharge. Long COVID was defined as the persistence of three or more COVID-19-related symptoms. The primary outcome of this study was the prevalence of long COVID after the period of COVID-19.

Results: During the study period, 290 patients were enrolled. Among them, 54.5 and 34.6% experienced long COVID within 6 months and after more than 18 months, respectively. Several patients showed abnormal results when tested

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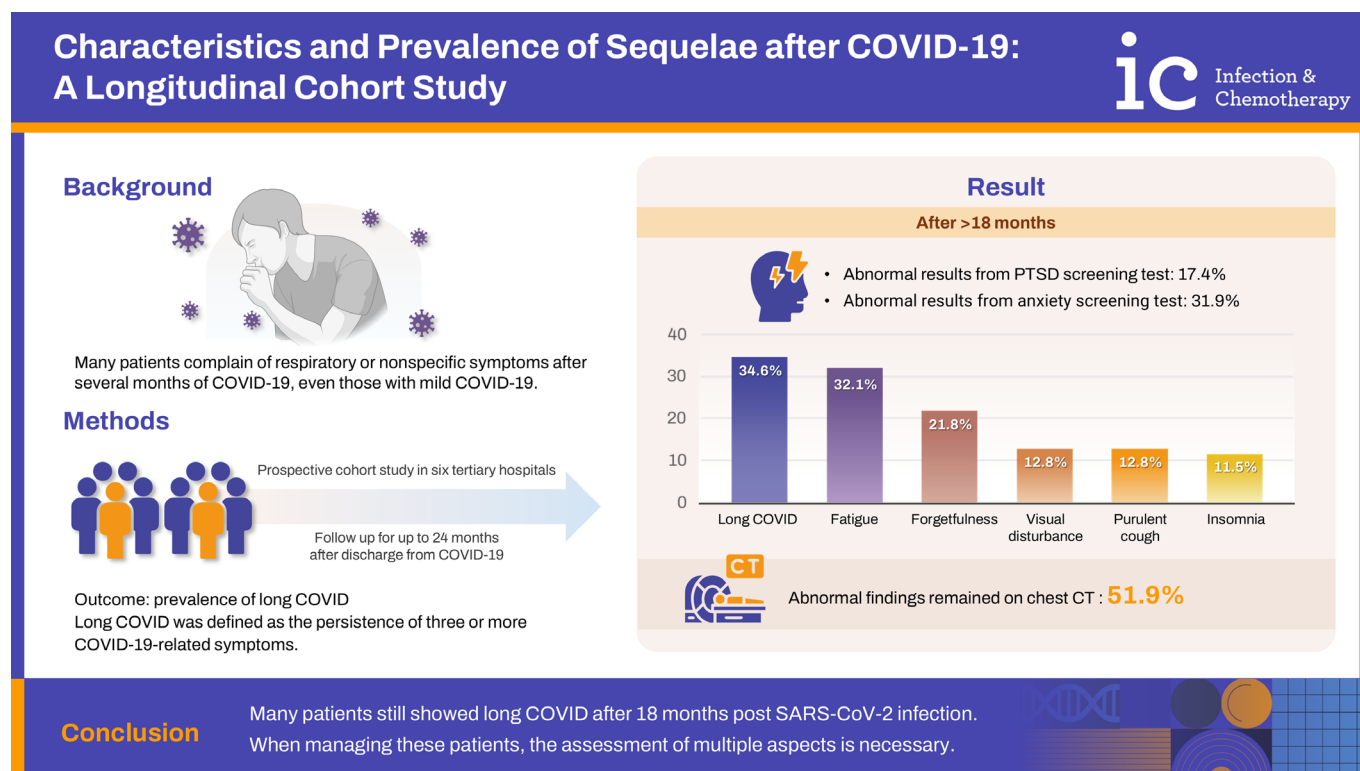
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for post-traumatic stress disorder (17.4%) and anxiety (31.9%) after 18 months. In patients who underwent follow-up chest computed tomography 18 months after COVID-19, abnormal findings remained at 51.9%. Males (odds ratio [OR], 0.17; 95% confidence interval [CI], 0.05-0.53; $P=0.004$) and elderly (OR, 1.04; 95% CI, 1.00-1.09; $P=0.04$) showed a significant association with long COVID after 12-18 months in a multivariable logistic regression analysis.

Conclusion: Many patients still showed long COVID after 18 months post SARS-CoV-2 infection. When managing these patients, the assessment of multiple aspects is necessary.

Keywords: COVID-19; Long COVID; Post-acute sequelae of SARS-CoV-2 infection; Post-COVID-19 condition

GRAPHICAL ABSTRACT



INTRODUCTION

In May 2023, the World Health Organization declared an end to the coronavirus disease 2019 (COVID-19) public health emergency [1]. However, this does not signify the end of COVID-19; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections continue to occur worldwide [2]. Several studies have reported that COVID-19-related sequelae may occur even after the acute phase of infection [3, 4]. Numerous patients complain of respiratory or nonspecific symptoms within several months of COVID-19, and more than 200 symptoms have been reported [5]. In addition, the prevalence of various

chronic illnesses, such as cardiovascular disease, diabetes, and chronic kidney disease has been reported to increase after COVID-19, thus highlighting the importance of understanding COVID-19-related sequelae [6-8]. The long-term effects of COVID-19 have been referred to as long COVID, post-acute sequelae of SARS-CoV-2 infection, post-COVID-19 condition, post-COVID syndrome, or long-haul COVID-19 [9]. Several studies have reported that patients with COVID-19 could experience long COVID regardless of disease severity [10, 11].

Although the severity and mortality rate of COVID-19 have relatively decreased, periodic resurgence may occur

owing to continued mutations in the SARS-CoV-2 spike protein [12]. In addition, even patients with mild COVID-19 can experience long COVID; therefore, the burden of long COVID is still considerable. Although variations exist among studies, the prevalence of long COVID ranges from 2.3–53%. In Korea, Kim et al. reported that 52.7% of patients experienced COVID-19-related symptoms even after 12 months post-infection [13, 14]. However, long-term and multifaceted research on long COVID, lacks. Therefore, in this study, we comprehensively analyzed post-COVID-19 clinical parameters, such as disease symptoms, laboratory tests, chest imaging, and pulmonary function, to further deepen our understanding of long COVID.

MATERIALS AND METHODS

1. Study design and patient population

We performed a prospective cohort study involving patients diagnosed with COVID-19 between February 2020 and September 2021 in six tertiary hospitals in Korea, covering the pre-Omicron period [15]; All enrolled patients agreed to participate in this study. Patients were followed up at 1, 3, 6, 12, 18, and 24 months after discharge from COVID-19. Laboratory tests and chest radiographs were performed and a questionnaire on the current conditions was administered at each visit. Pulmonary function tests (PFTs) and chest computed tomography (CT) scans were performed at 3 and 18 months after discharge. The questionnaire included the following items: persistent symptoms, Fatigue Severity Scale, K-PC-PTSD-5, GAD-7 score, EQ-5D-5L, EQ-VAS, modified Medical Research Council (mMRC) dyspnea scale, and lifestyle habits [16–20].

2. Ethics statement

This study was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Centre (4-2020-1403). Written informed consent was obtained from all the patients. The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its amendments.

3. Definition

Long COVID was defined as the persistence of three or more COVID-19-related symptoms, such as cough, dyspnea, and fatigue, for more than four weeks after COVID-19. The severity of acute COVID-19 episode was classified as follows; (1) “mild,” for patients with no oxygen demand; (2) “moderate,” for patients with oxygen supplied through a regular nasal cannula, and

(3) “severe,” for patients with oxygen supplied through a high-flow nasal cannula.

The K-PC-PTSD-5 questionnaire was used as a screening tool for post-traumatic stress disorder (PTSD); a score of ≥ 3 was deemed abnormal. The GAD-7 scale was used as a screening tool for anxiety; a score of ≥ 10 was deemed abnormal. The fatigue severity scale was used to evaluate fatigue; a score of ≥ 26 was deemed as having “significant” fatigue. Finally, abnormal chest CT images were defined as those with remaining or worsening COVID-19-related lesions as evaluated by a radiologist.

4. Outcomes

The primary outcome was the prevalence of long COVID after an acute COVID-19 episode. The secondary outcomes were as follows: (1) changes in PFTs, (2) abnormal psychiatric screening test results, and (3) risk factors for long COVID within 12–18 months post-infection.

5. Statistical analysis

The follow-up data of all patients were classified as follows: within 6 months, 6–12 months, 12–18 months, and ≥ 18 months after COVID-19. The participants in each period were divided into three groups according to COVID-19 the severity. Chi-square and Kruskal-Wallis tests were used to measure the differences between categorical and continuous variables among the study groups, respectively. The Bonferroni test was used for post-hoc multiple comparisons. Continuous variables were checked for normal distribution using the Shapiro-Wilk test. Multivariable logistic regression analyses were performed to assess the risk factors of long COVID. Variables with a P -value < 0.1 in univariate analyses or clinical relevance were entered into a multivariable model. All P -values were two-tailed; $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R V.4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 290 patients were enrolled during the study period. Among them, 176 patients were followed up as of October 2022. **Table 1** shows the characteristics of the study cohort. The median age of the study population was 59.5 years (interquartile range [IQR], 46–68 years) and 148 patients (51.0%) were men. Among the patients, 78 were in the mild COVID-19, 71 in the moderate, and 141 in the severe groups. Common symptoms among

the patients are shown in **Figure 1**. Within 6 months, 54.5% (104/191) of the patients experienced a long COVID. Although the disease proportion decreased over time, 34.6% (27/78) of the patients were found to have experienced long COVID even after 18 months; fatigue (25/78) was observed to be the most persistent symptom. Furthermore, a significant proportion of the patients complained of fatigue, forgetfulness, purulent cough, and visual disturbances, although the overall proportion of patients with persistent symptoms showed a decreasing trend over time. Patient sequelae profiles over time are shown in **Supplementary Table 1**. After 18 months, 30.8% (24/78) of the patients complained of significant fatigue according to the fatigue severity scale, whereas 23.1% (18/78) responded to a decrease in the mMRC dyspnea scale compared to their pre-COVID-19 profile. The comparative symptomatology according to severity for each period after COVID-19 is shown in **Supplementary Tables 2, 3, 4, and 5**.

The “mild” group was significantly younger than the other groups (41.0 years, 62.0 years, and 63.0 years) and had lower Charlson comorbidity (0.0, 2.0, and 2.0) and body mass index (BMI) (22.8 kg/m², 24.8 kg/m², and 25.1 kg/m²) and a significant proportion of patients had hypertension (11.5%, 33.8%, and 48.9%) and diabetes mellitus (6.4%, 29.6%, and 40.4%).

Changes in the PFT results according to the severity and period after the onset of COVID-19 symptoms are shown in **Supplementary Table 6**. The PFT results performed

within 6 months revealed that the “mild” group had significantly higher forced vital capacity (FVC) than the “severe” group (90.0%, IQR, 83.5–99.5 and 80.5%, IQR, 70.5–90.5; adjusted $P=0.003$). No difference in FVC was observed according to disease severity as per PFT performed after ≥ 18 months.

The psychiatric screening results for each period are shown in **Table 2**. Results revealed that after ≥ 18 months post-COVID-19, a significant proportion of patients had abnormal PTSD (17.4%, 12/69) and anxiety (31.9%, 22/69) screening tests. No significant differences were observed in disease severity (PTSD, Chi-square test, $P=0.551$; anxiety, $P=0.245$).

Laboratory test results during the study period are presented in **Supplementary Table 7**. On chest CT performed ≥ 18 months post-COVID-19, 51.9% (28/54) showed abnormal post-COVID-19-related findings (**Supplementary Table 8**). The proportion of patients with sequelae lesions on chest CT performed after 18 months was significantly higher in the “severe” group than that in the “mild” group (90.9% vs. 30.5%, respectively; adjusted $P=0.008$).

Multivariable logistic regression analysis was conducted to identify the factors associated with long COVID. Results revealed that males (odds ratio [OR], 0.17; 95% confidence interval [CI], 0.05–0.53; $P=0.004$) and elderly (OR, 1.04; 95% CI, 1.00–1.09; $P=0.04$) showed a significant association with long COVID after 12–18 months (**Table 3**).

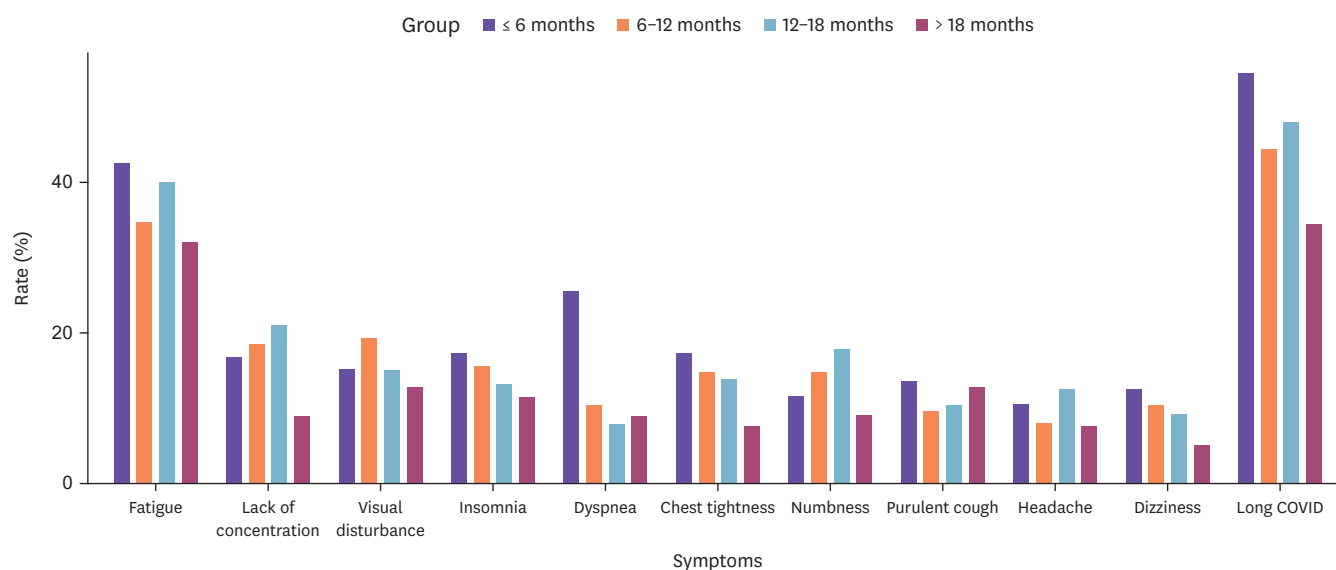


Figure 1. Most common symptoms persisting after COVID-19. COVID-19, coronavirus disease 2019.

Table 1. Clinical characteristics of cohort participants

Characteristics	Cohort (n=290)	Mild (n=78)	Moderate (n=71)	Severe (n=141)	P-value
Age (years)	59.5 (46.0–68.0)	41.0 (28.0–56.0)	62.0 (50.0–72.0)	63.0 (54.0–70.0)	<0.001
Sex, male	148 (51.0)	29 (37.2)	37 (52.1)	82 (58.2)	0.012
BMI (kg/m ²)	24.2 (22.2–27.0)	22.8 (20.8–24.4)	24.8 (22.9–26.8)	25.1 (22.9–27.8)	<0.001
At least 1 dose of vaccination before COVID-19	17 (5.9)	4 (5.1)	4 (5.6)	9 (6.4)	0.927
Comorbidities					
Hypertension	102 (35.2)	9 (11.5)	24 (33.8)	69 (48.9)	<0.001
Coronary artery disease	19 (6.6)	4 (5.1)	2 (2.8)	13 (9.2)	0.172
Heart failure	5 (1.7)	0	3 (4.2)	2 (1.4)	0.131
Diabetes mellitus	83 (28.6)	5 (6.4)	21 (29.6)	57 (40.4)	<0.001
Chronic lung disease	8 (2.8)	3 (3.8)	1 (1.4)	4 (2.8)	0.660
Chronic liver disease	5 (1.7)	0	1 (1.4)	4 (2.8)	0.299
Chronic kidney disease	13 (4.5)	2 (2.6)	1 (1.4)	10 (7.1)	0.110
Cerebrovascular accident	6 (2.1)	1 (1.3)	3 (4.2)	2 (1.4)	0.339
Solid cancer	18 (6.2)	6 (7.7)	7 (9.9)	5 (3.5)	0.162
Solid organ transplantation	3 (1.0)	0	2 (2.9)	1 (0.7)	0.198
Peptic ulcer disease	3 (1.0)	2 (2.6)	1 (1.4)	0	0.187
Dementia	1 (0.3)	0	0	1 (0.7)	0.588
Human immunodeficiency virus infection	2 (0.7)	2 (2.6)	0	0	0.065
Charlson comorbidity index	2.0 (0.0–3.0)	0.0 (0.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	<0.001

Continuous variables were described as median (interquartile range), and discrete variables were described as numbers (percentages). BMI, body mass index; COVID-19, coronavirus disease 2019.

Table 2. Psychiatric assessment after COVID-19 by period

Mild	Within 6 months (n=29)	6–12 months (n=18)	12–18 months (n=20)	After 18 months (n=29)
Significant in PTSD screening	4 (13.8)	6 (33.3)	4 (20.0)	4 (13.8)
Significant in GAD screening	15 (51.7)	6 (33.3)	6 (30.0)	9 (31.0)
Both significant	3 (10.3)	3 (16.7)	2 (10.0)	2 (6.9)
Moderate	Within 6 months (n=48)	6–12 months (n=22)	12–18 months (n=27)	After 18 months (n=25)
Significant in PTSD screening	4 (8.3)	5 (22.7)	4 (14.8)	6 (24.0)
Significant in GAD screening	22 (46.8)	7 (31.8)	6 (22.2)	6 (24.0)
Both significant	4 (8.3)	2 (9.1)	2 (7.4)	2 (8.0)
Severe	Within 6 months (n=96)	6–12 months (n=71)	12–18 months (n=67)	After 18 months (n=15)
Significant in PTSD screening	20 (20.8)	17 (23.9)	14 (20.9)	2 (13.3)
Significant in GAD screening	33 (34.4)	24 (33.8)	21 (31.3)	7 (50.0)
Both significant	16 (16.7)	14 (19.7)	10 (14.9)	2 (13.3)

Discrete variables were described as numbers (percentages). COVID-19, coronavirus disease 2019; PTSD, post-traumatic stress disorder; GAD, generalized anxiety disorder.

Table 3. Factors associated with long COVID after 12–18 months

Factors	Univariable analysis				Multivariable analysis			
	OR	2.50%	97.50%	P-value	OR	2.50%	97.50%	P-value
Male sex	0.20	0.10	0.40	<0.001	0.17	0.05	0.53	0.004
Age	1.02	1.00	1.05	0.037	1.04	1.00	1.09	0.040
Hemoglobin at 1 month after discharge	0.71	0.50	0.98	0.044	1.16	0.75	1.88	0.515
Severity of COVID-19 (Reference: mild)								
Moderate	0.63	0.26	1.52	0.307	0.24	0.05	1.02	0.061
Severe	1.05	0.48	2.29	0.902	0.33	0.08	1.24	0.113
At least 1 dose of vaccination	2.01	0.47	10.08	0.353	1.11	0.20	6.70	0.908
Diabetes mellitus	1.90	0.89	4.11	0.099				
Creatinine at 1 month after discharge	0.38	0.04	2.70	0.347				
Body mass index	0.97	0.89	1.04	0.422				
LDH at 1 month after discharge	1.00	0.99	1.00	0.599				
Chronic kidney disease	0.77	0.10	4.75	0.774				
Cancer	1.16	0.14	9.92	0.881				

COVID-19, coronavirus disease 2019; OR, odds ratio; LDH, lactate dehydrogenase.

DISCUSSION

We attempted to analyze the various aspects of long COVID by virtue of several factors, including clinical symptomatology, laboratory and diagnostic tests, PFTs, chest CT scans, and psychiatric screening, using a multicenter cohort follow-up observational study design throughout the study period. In this study, more than 50% of patients have experienced long COVID within 6 months after COVID-19 and more than 30% still experienced long COVID even after ≥ 18 months post-infection.

The prevalence of long COVID in our study is consistent with that of previous studies, although its definition varies among studies [13]. The respiratory symptoms tended to decrease over time. Although several studies have reported different persistence proportions, we considered that their decreasing proportions over time reflected an improvement in COVID-19-associated respiratory damage [14, 21, 22]. However, most patients with severe COVID-19 still had abnormal chest CT findings when performed >18 months post-infection, and no significant differences in the FVC and forced expiratory volume in 1 s of the PFTs were observed according to disease severity. Therefore, additional research is required to determine the association between abnormal chest CT findings and the long-term outcomes of respiratory sequelae.

Previous studies have reported the persistence of abnormal chest CT findings for several months post-infection [23, 24]. In this study, a significant proportion of patients showed abnormal lesions on chest CT post-COVID-19. Moreover, these findings persisted in 51.9% (28/54) of patients even after 18 months post-infection; most of those in the “severe” group showed such abnormalities (90.0%). Although most lesions were improving, this finding was consistent with the higher proportion of patients presenting with worsening mMRC in the “severe” group than those in the “mild” group (13.5% and 53.3%, adjusted $P=0.024$), as compared to their pre-COVID-19 profiles. Therefore, this result suggests that long-term follow-up and management are necessary for patients with severe COVID-19.

Several studies have reported that numerous patients with COVID-19 present with neuropsychiatric symptoms, including fatigue and insomnia [25]. Our study also showed that a significant proportion of patients experienced neuropsychiatric symptoms. Therefore, we used PTSD and anxiety screening tests to assess associated psychiatric disorders. We found that several

patients showed abnormal PTSD and generalized anxiety disorder screening test results regardless of the severity of COVID-19. Several studies have been conducted on the link between COVID-19 and psychiatric disorders; direct viral infection of the neuronal cells, astroglial inflammation, prolonged immune response, cytokine storms, and ischemia due to microvascular dysfunction or thrombosis were suggested as possible mechanisms [26]. Moreover, pandemic-related changes and stigma are believed to have contributed to the persistence of said symptoms [26]. The results of this study also suggest that a comprehensive approach is needed to managing patients with COVID-19, including various psychiatric, physical, and respiratory assessments.

Previous studies have reported the following risk factors for long COVID: age, female sex, obesity (BMI), presence of comorbidities, and COVID-19 severity [3, 4, 27, 28]. In the multivariable logistic regression analysis used in this study, female sex and older age were significantly associated with long COVID, which is consistent with previous studies. However, obesity, COVID-19 severity, and comorbidities were not significantly associated with long COVID. These differences were presumed to be due to variations in the definition of long COVID, cohort characteristics, and different ethnicities.

This study had several limitations. First, this study enrolled patients before the emergence of the Omicron variant, which eventually became a major concern. Thus, our cohort of participants might not accurately reflect the characteristics of current SARS-CoV-2 cases. The Omicron variant has been reported to cause less long COVID symptoms as compared to previous variants; however, the presenting symptoms were likely similar [29, 30]. Nonetheless, additional research including patients with recent variants of SARS-CoV-2 would deepen our understanding of the burden of sequelae after COVID-19 in Korea. Second, only a small proportion of cohort participants were vaccinated against SARS-CoV-2 before the onset of COVID-19. Vaccination not only prevents COVID-19 but also reduces its severity. Several studies have reported conflicting results regarding the protective effects of vaccination against long COVID [5, 31]. Our study could not investigate the association between vaccination and long COVID. Third, long COVID after a single COVID-19 or re-infection may show different characteristics. Further studies are needed as SARS-CoV-2 reinfection is becoming increasingly common [32]. Fourth, the inclusion of cases without all scheduled examinations

may have caused a bias. Nevertheless, we considered that demonstrating the analysis as comprehensively as possible would be appropriate for showing the sequelae related to COVID-19.

In this multicenter prospective cohort study, several patients were observed to suffer from long COVID even 18 months post-infection. Therefore, multiple assessments of various disease aspects are necessary for managing patients post-COVID-19.

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Conflict of Interest

JYC, HBK, and KRP are member of editorial board of *Infect Chemother*, however, they did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions

Conceptualization: YJB, JYC. Data curation: JK, JHJ, HS, WSC, DWP, YC, K-HS, ESK, HBK, JHK, KRP, JPC, JHK, HSK, HWJ. Formal analysis: SJL, YJB. Funding acquisition: JYC. Investigation: SJL, SHL, Jung Ho Kim, JYA. Methodology: SJL, YJB, JYC. Supervision: JYC. Validation: JYC. Writing - original draft: SJL, JYC. Writing - review & editing: SJL, YJB, SHL, JHK, JYA, JK, JHJ, HS, WSC, DWP, YC, KHS, ESK, HBK, JHK, KRP, JPC, JHK, HSK, HWJ, JYC.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Sequelae profile after COVID-19 according to the study period

Supplementary Table 2

Sequelae profile according to severity in the <6 months group

Supplementary Table 3

Sequelae profile according to severity in the 6-12 months group

Supplementary Table 4

Sequelae profile according to severity in the 12-18 months group

Supplementary Table 5

Sequelae profile according to severity in the ≥ 18 months group

Supplementary Table 6

Pulmonary function test after COVID-19 according to the study period

Supplementary Table 7

Laboratory test after COVID-19 according to the study period

Supplementary Table 8

Remaining lesions on chest computed tomography according to the study period

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