

## Prolonged and Late-Onset Symptoms of Coronavirus Disease 2019

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Some patients who recover from coronavirus disease 2019 (COVID-19) have prolonged symptoms such as dyspnea, fatigue, cough, and dysosmia for longer than 120 days after symptom onset. In addition, some patients who recovered from COVID-19 reported hair loss a few months after the onset of the disease. Alopecia is a late-onset symptom of COVID-19. The cause of alopecia is unknown; however, androgenic alopecia and telogen effluvium are possible causes.

**Keywords:** alopecia; COVID-19; duration; late-onset symptoms; prolonged symptoms.

Prolonged symptoms after coronavirus disease 2019 (COVID-19) recovery have been a social concern. Although previous studies have investigated post-COVID-19 symptoms 14–21 days after diagnosis [1] and approximately 60 days after symptom onset [2], no studies have shown a longer progression of symptoms than these studies. In addition, few previous studies have investigated COVID-19-related late-onset symptoms that tend to emerge after recovery [1]. Androgenetic alopecia was present in the majority of hospitalized patients with COVID-19 [3], and acute telogen effluvium associated with severe acute respiratory syndrome coronavirus 2 infection was reported [4]; however, alopecia as a late-onset symptom has not been reported to date. In this study, we investigated the duration of persistent symptoms and late-onset symptoms including alopecia in patients who were discharged from the National Center for Global Health and Medicine (NCGM) after recovery from COVID-19.

Received 21 September 2020; editorial decision 12 October 2020; accepted 14 October 2020.  
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Open Forum Infectious Diseases® 2020

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DOI: 10.1093/ofid/ofaa507

## METHODS

### Study Participants and Study Period

Patients who were admitted due to COVID-19 at the Disease Control and Prevention Center (DCC) and the NCGM and who were discharged between February 2020 and June 2020 were invited to the telephone interviews. Patients who died during admission or their family were not invited to participate in the interviews. The telephone interviews were conducted from July 30, 2020 to August 13, 2020.

### Patient Consent Statement

Written informed consent was obtained from all patients. This study was reviewed and approved by the Ethics Committee of the Center Hospital of the NCGM (NCGM-G-003472-03).

### Study Method

As part of outpatient follow-up support, the investigators (M.A., Y.M., M.T., Y.O., S.M., K.T.) conducted one-on-one structured individual telephone interviews with the patients. Each interview lasted approximately 5–10 minutes, and each patient was interviewed once. The investigators were nurses, researchers, and physicians working in the DCC and NCGM.

### Items Investigated

Information obtained from participants included age, sex, ethnicity, smoking history, history of alcohol use, body mass index (BMI), medical conditions, abnormalities on imaging studies, respiratory failure status, mechanical ventilation status, extracorporeal membrane oxygenation requirements, and medications (antivirals, corticosteroids, and anticoagulants). Accurate information regarding clinical and laboratory parameters was stored in the electronic files of each participant, which were retrieved for analysis.

In the one-on-one structured individual telephone interviews, participants were asked about symptoms and symptom duration on admission. For alopecia, we asked whether participants ever felt that their hair fell out more easily after recovery. They were also asked about when they felt their hair was falling out more easily. The investigators double-checked the symptoms with each participant by checking the electronic files. They were also asked about other symptoms including alopecia, which they noticed after discharge, and its duration. If they were not able to recall symptom duration, the answers were regarded as missing values.

## RESULTS

A total of 78 patients were potentially eligible for follow-up telephone interviews. Of these, 2 died after discharge. We could not

complete interviews with 3 patients due to dementia and could not get through to 10 patients. Thus, 63 patients completed the interviews. The demographic and clinical characteristics of the participants are summarized in Table 1. Twenty-one patients

**Table 1. Demographic and Clinical Characteristics of the Participants (n = 63)**

Characteristics	Value
Age, mean (SD), years	48.1 (18.5)
Female sex, no. (%)	21 (33.3)
Body mass index, mean (SD) <sup>a</sup>	23.7 (4.0)
Ethnicity, no. (%)	
Japanese	56 (88.9)
Chinese	3 (4.8)
Bangladeshi	1 (1.6)
Vietnamese	1 (1.6)
American	1 (1.6)
French	1 (1.6)
Smoking history, no. (%) (12 missing)	
Yes	23 (45.1)
No	28 (54.9)
Alcohol use, no. (%) (14 missing)	
Yes	31 (63.3)
No	18 (36.7)
No. of medical conditions, no. (%)	
0	37 (58.7)
1	11 (17.5)
2	7 (11.1)
≥3	8 (12.7)
Individual medical conditions, no. (%)	
Hypertension	16 (25.4)
Dyslipidemia	16 (25.4)
Diabetes	9 (14.3)
Connective tissue disease	3 (4.8)
Cerebrovascular disease	2 (3.2)
Bronchial asthma	1 (1.6)
Congestive heart failure	1 (1.6)
Solid tumor	1 (1.6)
Peripheral artery disease	1 (1.6)
HIV/AIDS	1 (1.6)
Acute COVID-19 characteristics, no. (%)	
Pneumonia diagnosed	47 (74.6)
Oxygen supplementation	
Oxygen therapy	17 (27.0)
Mechanical ventilation	5 (7.9)
ECMO	0 (0.0)
Pharmacological treatments	
Antiretroviral	29 (46.0)
Corticosteroids	9 (14.3)
Anticoagulant	7 (11.1)
Length of hospital stay, mean (SD), days	14 (10.0)
Point-by-telephone interview	
Days since symptom onset, mean (SD)	129 (21)
Days since discharge: mean (SD)	108 (23)

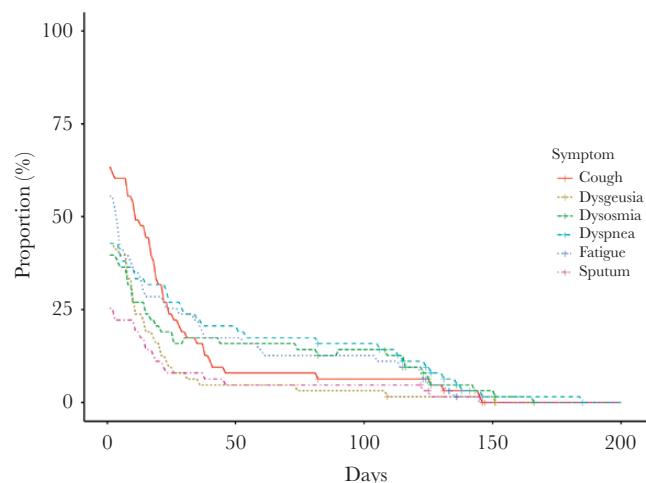
Abbreviations: AIDS, acquired immunodeficiency syndrome; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; SD, standard deviation.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

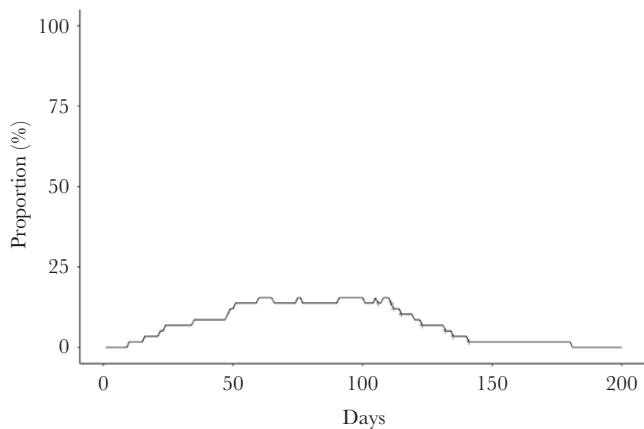
(33.3%) were women. The mean age was 48.1 years (standard deviation [SD] = 18.5). Fifty-six patients (88.9%) were Japanese, followed by Chinese (n = 3, 4.8%), Bangladeshi (n = 1, 1.6%), Vietnamese (n = 1, 1.6%), American (n = 1, 1.6%), and French (n = 1, 1.6%). The mean BMI was 23.7 (SD = 4.0). Forty-seven patients (74.6%) had pneumonia. Seventeen patients (27.0%) received oxygen therapy, 5 patients (7.9%) were on mechanical ventilation, and 29 patients (46%) were on antivirals. Missing values ranged from 0% to 22.2%.

The participants' prolonged symptoms and duration are summarized in Figure 1. The numbers of patients with fever, cough, fatigue, dyspnea, dysgeusia, dysosmia, sputum production, and chest pain at the time of symptom onset were 45 (71.4%), 40 (63.5%), 35 (55.6%), 27 (42.9%), 27 (43.5%), 1 missing, 25 (40.3%), 1 missing, 16 (25.4%), and 6 (9.5%), respectively. Fever resolved within 30 days (range, 0–27; mean, 7.4 days; SD = 7.0) in all participants. A high proportion of participants reported prolonged symptoms: cough (n = 5, 7.9%), fatigue (n = 10, 15.9%), dyspnea (n = 11, 17.5%), dysgeusia (n = 3, 4.8%, 1 missing), and dysosmia (n = 10, 16.1%, 1 missing) 60 days after symptom onset, and cough (n = 4, 6.3%), fatigue (n = 6, 9.5%), dyspnea (n = 7, 11.1%), dysgeusia (n = 1, 1.6%, 1 missing), and dysosmia (n = 6, 9.7%, 1 missing) 120 days after symptom onset. All of these symptoms were not chronic symptoms before the onset of COVID-19, but they were sequelae related to COVID-19.

For late-onset symptoms, 2 participants reported dysosmia 30 and 92 days after symptom onset. None of the participants reported any other late-onset symptoms other than alopecia. Figure 2 shows the proportion of patients who developed alopecia after discharge. Fourteen (24.1%) of 58 patients (5 missing) reported alopecia. Of the 14 patients, 5 were women and 9 were men. The mean time from COVID-19 symptom onset to the emergence of alopecia was



**Figure 1.** Proportion of patients who presented symptoms after admission (n = 63).



**Figure 2.** Proportion of patients who presented alopecia after admission (n = 58).

58.6 days (SD = 37.2). Among the 14 patients, alopecia resolved in 5 patients. The mean duration of alopecia among the 5 patients was 76.4 days (SD = 40.5). The remaining 9 patients still had alopecia at the time of the interview. The mean duration of alopecia among the 9 patients was 47.8 days (SD = 32.2).

## DISCUSSION

We investigated the duration of persistent symptoms and late-onset symptoms, including alopecia, in patients with COVID-19. The most important findings throughout this study were dyspnea (n = 7, 11.1%), fatigue (n = 6, 9.5%), cough (n = 4, 6.3%), dysosmia (n = 6, 9.7%), and dysgeusia (n = 1, 1.6%) that persisted for more than 120 days after symptom onset, whereas fever was the most frequent symptom (n = 45, 71.4%) at the onset of the disease. Further research is needed to identify the risk factors contributing to long-term persistence of symptoms and to clarify whether treatment for COVID-19 may reduce the incidence or shorten the duration of post-COVID-19 symptoms.

The second important finding was that 24.1% of patients with COVID-19 reported alopecia 58.6 days (mean SD = 37.2) after symptom onset, and that the mean duration of alopecia was 76.4 days. Alopecia is frequently observed in other post-viral infections such as Ebola virus disease and dengue fever

[5, 6]. The cause of alopecia after recovering COVID-19 is unknown; however, androgenic alopecia and telogen effluvium are possible causes [3, 4].

The findings of this study are subject to several limitations. First, this study relied on patient self-reports and therefore might have been subject to recall bias. Second, those with more severe symptoms might have been less likely to respond to telephone calls if they were subsequently hospitalized or unable to answer the telephone, making data on the critically ill more likely to be scarce. Third, this was a single-center study with a small sample size. Finally, some patients still had prolonged symptoms at the time of the interview. Continual monitoring of long-lasting symptoms is needed to obtain a more accurate duration of prolonged symptoms.

## CONCLUSIONS

Some patients who recover from COVID-19 have prolonged symptoms such as dyspnea, fatigue, cough, and dysosmia. Alopecia is a late-onset symptom of COVID-19.

## Acknowledgments

**Financial support.** This work was funded by the Health, Labor and Welfare Policy Research Grants, Research on Emerging and Reemerging Infectious Diseases and Immunization (Grant Number 20HA1006).

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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