Persistent Symptoms in Patients Recovering From COVID-19 in Denmark

Steffen Leth,[1,] Jesper Damsgaard Gunst,[1,2] Victor Mathiasen,[1] Kristoffer Hansen,[1] Ole Søgaard,[1,2] Lars Østergaard,[1,2] Søren Jensen-Fangel,[1] Merete Storgaard,[1] and Jane Agergaard[1]

[1]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark, and [2]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

Background. Although persistent symptoms after coronavirus disease 2019 (COVID-19) are emerging as a major complication to the infection, data on the diversity and duration of symptoms are needed.

Methods. Patients aged ≥18 years with a positive polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 who were hospitalized at the Department of Infectious Diseases, Aarhus University Hospital, Denmark, in the period from March 11 to May 15 were offered follow-up after hospitalization. On admission, a comprehensive symptom and medical history was collected, including demographic characteristics, duration of symptoms, comorbidities, and concomitant medications. At discharge, patients were offered follow-up consultations—either by telephone or at an in-person visit—at 6 and 12 weeks at our post-COVID-19 outpatient clinic to assess whether symptoms present at admission had resolved.

Results. During the inclusion period, 71 patients were admitted with COVID-19. Of these, 10 patients died, 3 were transferred to another region, 4 declined to participate, and 5 were lost to follow-up before the 12-week evaluation. Thus, 49 patients were included. Overall, 96% reported 1 or more persisting symptoms at 12-week follow-up. The main symptoms were fatigue, dyspnea, cough, chemosensory dysfunction, and headache.

Conclusions. A wide range of persistent symptoms in patients recovering from COVID-19 were present 12 weeks after hospitalization, calling for larger descriptive studies and interdisciplinary research collaborations.

Keywords. COVID-19; post-COVID-19; SARS-CoV-2.

As of January 6, 2021, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has infected more than 86 million individuals globally, spread across 191 countries, causing more than 1 million related deaths [1]. In Denmark, 3 979 917 individuals have been tested for SARS-CoV-2 as of January 6, 2021. Of those, 172 779 individuals tested positive, 142 057 have recovered from infection, and 1420 (0.8%) individuals have died of COVID-19 [2].

The variation in symptomatology and severity during hospitalization with COVID-19 quickly became known during the first wave of the pandemic. The clinical features ranges from being asymptomatic to having severe pneumonia and multiorgan failure with need of intensive care treatment [3–5]. Emerging data suggest that COVID-19 can result in long-term symptoms from several organ systems in a subgroup of individuals recovering from acute infection. The primary reported long-term symptoms include cognitive impairment, fatigue, chest pain, dyspnea, cough, and impaired smell and taste [6–8]. These findings raise important major questions about the long-term health consequences of COVID-19. Thus, we are in urgent need of more evidence about the duration of organ-specific symptoms and complications that appear after the initial phase of COVID-19, including data from hospitalized and nonhospitalized patients, in order to describe and understand the full spectrum of COVID-19. Finally, these data will inform public health and social policy tailoring. In this study, we demonstrate diverse persistent symptoms 12 weeks after discharge in adult patients with COVID-19.

METHODS

Patients eligible for inclusion were hospitalized at Aarhus University Hospital, Denmark. Aarhus University Hospital has a catchment area of 300 000 citizens and has ~850 beds. The Department of Infectious Diseases has 22 beds and an outgoing consultant function at the hospital. All patients suspected of COVID-19 are admitted via the emergency department for clinical evaluation and transferred to the Department of Infectious Diseases if in need of oxygen support. The Infectious Diseases Department currently

functions solely as a COVID ward where the bed capacity is adapted to the need. In addition, the ward receives the most critically ill COVID-19 patients from nearby hospitals, including patients in need of extra corporal membrane oxygenation via the intensive care unit.

On admission to the emergency department, patients with fever and respiratory symptoms were screened with a polymerase chain reaction (PCR) test for SARS-CoV-2. Patients aged 18 years or older with a positive test who had been hospitalized for at least 12 hours and who had been transferred from the emergency department to the Department of Infectious Diseases were eligible.

In this report, we describe patients hospitalized between March 11 and May 15, during the first wave of the COVID-19 epidemic in Denmark. On admission, a comprehensive symptom and medical history was obtained and registered in the patient journal, including duration of symptoms, demographic characteristics, comorbidities, and concomitant medication. After discharge, patients were offered follow-up consultations. The first consultation was by telephone at ≥6 weeks, and the second consultation was by in-person visit or telephone at ≥12 weeks. Data analyses were done corresponding to days 42 and 84—that is, how many reported a specific symptom on days 42 and 84, respectively, after discharge.

Here patients were interviewed according to a COVID-19-specific, structured interview guide addressing organ-specific symptoms to assess whether the symptoms present at admission had resolved or new symptoms had emerged (Supplementary Data). The interview guide was designed to identify and systematically record previous and current symptoms (Table 2). Cognitive function was assessed by the validated orientation, memory, and concentration (OMC) test [9]. An OMC score of ≤24 was interpreted as impaired. Patients with dyspnea were asked whether they had dyspnea at rest, when walking, when walking uphill, or during strenuous physical activity. Severe dyspnea was defined as dyspnea at rest or when walking (equaling a Medical Research Council dyspnea score of 3–5) [10]. An individual interdisciplinary assessment was subsequently offered if needed. Data were analyzed using Stata Intercooled, version 11. We used multivariate logistic regression analysis to identify independent risk factors for persistent COVID-19 symptoms. For calculation of odds ratios (ORs) for risk factors of persistent symptoms, logistic regression was used. Covariates included in the multivariate logistic regression model were age, sex, body mass index (BMI), comorbidity, and smoking. P values <.05 were considered statistically significant.

Patient Consent Statement

Each patient provided written informed consent. All data were registered in a secure REDCap database hosted at the Clinical Trial Unit, Aarhus University [11]. Data collection was approved by the Central Denmark Region (reference 1-45-70-5-20). The registry- and questionnaire-based design did not require ethical approval (Danish Committee Act, Section 14, Subsection 2), which was confirmed by the Regional Ethics Committee (reference 1-10-72-181-20).

RESULTS

Between March 11 and May 15, 71 patients were admitted to our department. Of these, 7 patients died in the hospital, 3 died 1–6 weeks after discharge from the hospital, and 3 were transferred to another region and were therefore not eligible for the study. Of 58 eligible patients, 4 subsequently declined follow-up, and 5 were lost to follow-up before 12-week evaluation. Thus, 49 patients contributed with full data and were included in the study.

The median age (interquartile range [IQR]) of the 49 patients included was 58 (43–78) years, and 57% (n = 28) were female. The majority of the patients were Caucasian (86%, n = 42). The median number of days from onset of symptoms to hospitalization (IQR) was 8 (4–10) days, and patients were hospitalized for a median (IQR) of 6 (3–10) days. Six patients (12%) required intensive care treatment during their hospitalization. Patients had a median BMI (IQR) of 27.5 (24.5–32.7) kg/m^2, 63% never smoked, and 63% had ≥1 comorbidities, with hypertension being the most prevalent. The study population is summarized in Table 1.

Symptoms during hospitalization and at subsequent follow-up consultations are summarized in Table 2. The first follow-up consultation was performed at a median (IQR) of 51 (46–59.5) days after discharge, and the second follow-up consultation was performed at a median (IQR) of 128 (98–148) days.

At hospitalization, the most common symptoms registered were cough (92%), fatigue (63%), dyspnea (61%), headache (48%), and myalgia (47%). Symptoms from the gastrointestinal system also predominated, with 39% reporting nausea, 37% reporting diarrhea, and 20% reporting abdominal pain. Further, 11% and 17% reported smell and taste impairment, respectively.

A data analysis performed corresponding to day 42 showed that 86% reported the presence of 1 or more symptoms. The most frequent symptoms were fatigue (65%), dyspnea (53%), subjective difficulties concentrating (39%), and impaired smell (35%) and taste (33%). Overall, 51%, 69%, and 18% reported symptoms that could originate from the central and peripheral nervous, cardiopulmonary, and gastrointestinal systems, respectively.

A data analysis performed corresponding to day 84 showed that 96% reported the presence of 1 or more symptoms. Consistent with findings at the first follow-up consultation, the predominating symptoms were fatigue (63%), dyspnea (53%), and difficulties concentrating (45%). Measures of severity of symptoms tended to decrease from the first to second consultation: Impaired OMC test decreased from 21% to 11% (8/32 vs 4/32; relative risk [RR], 2.00; 95% CI, 0.66–6.09; P = .21)

and severe dyspnea from 42% to 22% (10/24 vs 4/18; RR, 1.88; 95% CI, 0.70–5.03; $P = .19$). Several symptoms showed an increasing prevalence during the follow-up period, such as paresthesia (27%; $P = .22$), chest pain (20%; $P = .15$), and myalgia (35%; $P = .04$), although not all were significant using the chi-square test.

Overall, 57%, 67%, and 16% reported symptoms originating from the central and peripheral nervous, cardiopulmonary, and gastrointestinal systems, respectively.

Altogether, these data suggest the long-term persistence of COVID-19-related symptoms.

Age, BMI, smoking, and comorbidities are known predisposing factors for severe COVID-19 [12–15]. Using multivariate logistic regression analyses, we evaluated the covariates age, BMI, smoking, and comorbidities as potential independent risk factors for the most common persistent symptoms: fatigue, dyspnea, and difficulty concentrating. We calculated the OR for fatigue, dyspnea, and impaired concentration based on each of these potential risk factors: age over vs under 60 years, BMI over vs under 25 kg/m^2, smoker and previous smoker vs nonsmoker, and comorbidity vs no comorbidity. Here we found a significantly reduced OR of difficulty concentrating if the patient was a current (or previous) smoker. Besides that, we found no significant OR for persistent symptoms following admission for COVID-19 for any of the other listed known risk factors for severe COVID-19 (Supplementary Table 1).

DISCUSSION

Among 49 patients included in this cohort study, a concerning 86% and 96% reported the presence of 1 or more symptoms at 6- and 12-week follow-up, respectively, after onset of COVID-19-related symptoms.

The primary persistent symptoms at 6- and 12-week follow-up were fatigue, dyspnea, impaired concentration, cough, and impaired smell and taste, consistent with the literature so far.

Symptoms after hospitalization were reported in an early study including 143 patients discharged after COVID-19 from the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy [6]. The patients were assessed in an outpatient clinic at a mean (SD) of 60.3 (13.6) days after the onset of the first COVID-19 symptom. Only 13% were free of any COVID-19-related symptoms, while 32% had 1 or 2 symptoms and 55% had 3 or more. As in our study, the dominating symptoms were fatigue, dyspnea, arthralgia, chest pain, and cough.

A few studies have addressed persistent symptoms in nonhospitalized patients. In a multicenter study from the United States, 292 nonhospitalized patients were contacted 7–21 days after a positive SARS-CoV-2 PCR test. They found that 92% had symptoms at the time of the test, and 35% of these

Table 1.   Demographic and Clinical Characteristics

Characteristics	Value
Total No. of patients	49
Age, median (IQR), y	58 (48–73)
Sex, No. (%)	
Female	28 (57)
Male	21 (43)
Ethnic origin, No. (%)	
Caucasians	42 (86)
African Danish	2 (4)
Middle East	4 (8)
Other	1 (2)
Days from onset of symptoms to hospitalization, median (IQR)	8 (4–10)
Respiratory rate/min at hospitalization, median (IQR)	22 (20–27)
Transcutaneous saturation at hospitalization, median (IQR), %	95 (93–96)
Maximum oxygen requirement, No. (%)	
No oxygen requirement	11 (22)
Nasal cannula	30 (61)
High-flow nasal cannula	3 (6)
Invasive mechanical ventilation	5 (10)
Intensive care unit admission during hospitalization, No. (%)	6 (12)
Duration of hospitalization, median (IQR), d	6 (3–10)
BMI, 48 pt.	
Median (IQR), kg/m^2	27.5 (24.5–32.7)
<25 kg/m^2, No. (%)	17 (35)
≥25–<30 kg/m^2, No. (%)	14 (29)
≥30–<35 kg/m^2, No. (%)	9 (19)
≥35 kg/m^2, No. (%)	8 (17)
Smoking status, 48 pt., No. (%)	
Never	30 (63)
Former	14 (29)
Current	4 (8)
Comorbidity, No. (%)	
None	18 (37)
≥1	31 (63)
Hypertension	14 (29)
Cancer	6 (12)
Coronary heart disease	5 (10)
Asthma	4 (8)
COPD	4 (8)
Diabetes	2 (4)
Hyperthyroidism	2 (4)
Cerebrovascular disease	1 (2)
Other[a]	5 (10)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a]Gout, lymph node tuberculosis, pulmonary/cardiac sarcoidosis, psoriasis, granulomatosis with polyangiitis.

still had symptoms at a telephone interview (median, 16 days after the time of the test)—primarily driven by fatigue, cough, headache, and shortness of breath [16]. These early findings should merit equal attention and resources allocated to follow and assess both hospitalized and nonhospitalized patients for persistent symptoms following COVID-19.

Table 2.   COVID-19-Related Symptoms at Baseline, 6 Weeks, and 12 Weeks

	Baseline, Hospitalization	Symptoms Reported 42 d After Discharge (6 wk)	Symptoms Reported 84 d After Discharge (12 wk)
	No. Patients/ Total (%)	No. Patients/Total (%)	No. Patients/Total (%)
Cognitive assessment			
Difficulties concentrating	NA	19/49 (39)	22/49 (45)
Impaired OMC test[a]	NA	8/38 (21)	4/38 (11)
Central and peripheral nervous system			
Paresthesia	NA	8/49 (16)	13/49 (27)
Headache	23/48 (48)	12/49 (24)	13/49 (27)
Smell impairment	5/47 (11)	17/49 (35)	13/49 (27)
Taste impairment	8/47 (17)	16/49 (33)	15/49 (31)
≥1 C/PNS symptom(s)	-	25/49 (51)	28/49 (57)
Cardiopulmonary system			
Dyspnea	30/49 (61)	26/49 (53)	26/49 (53)
Severe dyspnea[b]	NA	10/24 (42)	4/18 (22)
Cough	45/49 (92)	15/49 (30)	12/49 (24)
Expectoration	18/48 (38)	7/49 (14)	6/49 (12)
Chest pain	7/41 (17)	5/49 (10)	10/49 (20)
Nasal congestion	3/48 (6)	7/49 (14)	4/49 (8)
Sore throat	8/47 (17)	9/49 (18)	5/49 (10)
≥1 CPS symptom(s)	-	34/49 (69)	33/49 (67)
Gastrointestinal system			
Reduced appetite	NA	8/49 (16)	2/49 (4)
Nausea	19/49 (39)	2/49 (4)	4/49 (8)
Abdominal pain	10/49 (20)	1/49 (2)	5/49 (10)
Diarrhea	18/49 (37)	1/49 (2)	4/49 (8)
≥1 GIS symptom(s)	-	9/49 (18)	8/49 (16)
Other			
Fatigue	30/48 (63)	32/49 (65)	31/49 (63)
Myalgia	23/49 (47)	8/49 (16)	17/49 (35)
Fever (≥38°C)	36/49 (73)		
Subjective reported fever		1/49 (2)	2/49 (4)
All			
≥1 symptom(s) (C/PNS, CPS, GIS)		42/49 (86)	47/49 (96)

Abbreviations: C/PNS, central/peripheral nervous system; COVID-19, coronavirus disease 2019; CPS, cardiopulmonary system; GIS, gastrointestinal system; IQR, interquartile range; OMC, orientation, memory, and concentration.

[a]Orientation, memory, and concentration were assessed by the orientation, memory, and concentration (OMC) test [9].

[b]Severe dyspnea was defined as dyspnea at rest or when walking (Medical Research Council dyspnea score 3–5) [10].

Focusing on the different organ systems, we found that 69% and 67% had 1 or more symptoms originating from the cardiopulmonary system at 6- and 12-week follow-up, with dyspnea, cough, and chest pain being the main dominating complaints. In line with these findings, a recent observational cohort study of 100 patients who had recovered from COVID-19 showed that 78 patients had abnormal findings on cardiovascular magnetic resonance imaging (MRI) and 60 patients showed signs of ongoing inflammation at a median of 71 days after diagnosis. Thirty-six percent of the cohort reported dyspnea and unusual fatigue [17]. These findings were substantiated in a study examining the heart by MRI of 26 SARS-CoV-2-positive athletes who did not require hospitalization [18]. Here, 46% had evidence of myocarditis or prior myocardial injury 12–53 days after their positive test result. Similar reports have emerged on pulmonary sequelae in patients recovering from COVID-19 with persistent symptoms and radiologic abnormalities, consistent with reports of pulmonary dysfunction months after the acute phase of COVID-19 [19, 20].

We found that 51% and 57% had 1 or more symptoms potentially originating from the central and peripheral nervous system at the 2 follow-up time points. The dominating symptoms here were headache, paresthesia, and chemosensory dysfunction (smell and taste impairment). Some of these post-COVID-19 symptoms resemble those of patients recovering from, for example, encephalitis, and to some degree meningitis. It has been suggested that coronaviruses are able to reach the central nervous system through hematogenous or neural propagation possibly through the olfactory nerve—which, in part, could explain chemosensory dysfunction [21–23]. In line with

our observations, minor neurological manifestations have been reported in SARS-CoV-2-positive patients, such as headache, confusion, and "brain fog" [23], but more severe neurological manifestations, such as cerebral ischemic stroke, cerebral perfusion abnormalities, and leptomeningeal enhancement, have also been described [24].

Persisting symptoms from multiple organs could reflect the wide distribution of the preferred SARS-CoV-2 host receptor, angiotensin-converting enzyme 2 (ACE 2), in different tissues such as the epithelium of the intestine, the kidneys and blood vessels, the endothelial cells in the lungs, and the endothelial cells in the central nervous system [12, 25, 26]. As viral replication accelerates, epithelial–endothelial barrier integrity is compromised, accentuating the inflammatory response, which may explain the lymphocytic endotheliitis observed in a postmortem pathological examination of the heart, kidney, liver, and lungs in patients who died of COVID-19 [27–30]. This inflammatory phase could contribute to the wide range of persistent symptoms in patients recovering from COVID-19.

Persistent symptoms following other coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), are also well described. A recent meta-analysis described the clinical long-term outcomes of adult SARS and MERS survivors. The meta-analysis included 28 studies and 2820 patients. Pooled analysis revealed that several complications were common up to 6 months after discharge, such as lung function abnormalities (27%) and psychological impairment including post-traumatic stress disorder (38%), depression (33%), and anxiety (30%), as well as reduced exercise capacity and health-related quality of life [31]. Given that SARS and MERS belong to the same family of viruses as SARS-CoV-2, lessons learned from long-term sequalae following MERS and SARS should help guide clinicians in how to monitor the range of physical and mental health impairments in patients suffering from persistent symptoms following COVID-19.

In our study, we tended to find more patients with paresthesia and difficulties concentrating at 12 weeks compared with 6 weeks after discharge from the hospital. Cognitive impairment and neurological sequalae are also frequently observed in other patient groups recovering from severe infectious diseases. In a study of 516 older severe sepsis survivors (mean age, 76.9 years), severe sepsis was found to be associated with a nearly 3-fold increase in the odds of moderate to severe cognitive impairment after discharge and further emergence of new symptoms after discharge, as compared with 4517 patients who survived a nonsepsis hospitalization [32].

In our study, though the number of patients was small, we found a significantly reduced OR of challenged concentration if the patient was a current (or previous) smoker. Smoking has previously been associated with cognitive impairment [33], although this finding remains to be addressed in large-scale studies. Besides this, we found no increased OR of persistent

symptoms 12 weeks after the acute phase of COVID-19 when looking at risk factors such as age, sex, BMI, or comorbidity, emphasizing that persistent symptoms can occur in previously healthy young people. However, in a large prospective cohort study from New York including 5279 patients admitted with COVID-19, older age, high BMI, and multimorbidity were associated with not returning to a usual state of health 14–21 days after detection of SARS-CoV-2 [34].

Unfortunately, we did not systematically collect data on quality of life or whether patients had returned to their baseline health after hospitalization for COVID-19. In a recent study, 120 COVID-19 patients were interviewed by phone at a mean of 110.9 days after discharge. Of the active workers (56 patients), 38 patients had gone back to work at the time of the phone interview, and further, among the 39 patients who regularly participated in sports activities before their hospitalization with COVID-19, 28 patients had been able to resume physical activity, but at a lower level for 18 patients [35]. Similarly, in another study, 100 patients discharged after hospitalization for COVID-19 were interviewed by phone 4–8 weeks after discharge (mean, 48 days) using the European Quality of life - 5 Dimensions (EQ-5D) screening tool to assess mobility, personal care, usual activities, pain, and anxiety/depression. Of the 100 included patients, 68 were managed in hospital wards without needing intensive care unit (ICU) care (ward group). Here a clinically significant drop in EQ5D in 68.8% of the ICU group and 45.6% of the ward group was observed, suggesting prolonged recovery in terms of quality of life [36].

It should be noted that we became increasingly aware of symptoms present at follow-up that were not systematically registered during primary admission or initially during follow-up, which is why these findings are not systematically reported here. These symptoms include heart palpation, burning sensation in the chest, dizziness, memory loss, muscle weakness, fluctuating skin rash, and hair loss.

Finally, the benefit of using a clinical multidisciplinary follow-up setting to reduce long-term consequences of critical illness could prove important to patients suffering from persistent symptoms after the acute phase of COVID-19. In a randomized clinical trial including 291 patients recovering from sepsis, patients were randomized to either standard care, provided by their primary care physician (PCP), or standard care plus patient training, case management provided by trained nurses, and clinical decision support for PCPs by consulting physicians. Although there was no significant difference in mental health–related quality of life at 6 months (the primary outcome), the intervention group experienced improvements in several secondary outcomes related to physical function and disability and experienced fewer sleep impairments [37].

The documented high prevalence of symptoms after COVID-19, in a population with a growing number of affected individuals, may have huge health and socioeconomic consequences.

Neither the pathogenesis nor the organs involved are clear. Caring for these patients will require a multidisciplinary approach in specialized centers in which investigation and treatment are continuously adjusted to new knowledge, where guidance of health care workers who are not familiar with the condition could be performed.

Though we illustrate the presence of persistent symptoms through a systematic interview, some limitations should be acknowledged. First is the small, homogeneous sample size. Second is the single-center setup; our findings will need confirmation on a larger scale. Third is the lack of a control group. Fourth is the lack of objective measurements. Fifth, these data only address hospitalized patients, and potential persistent symptoms following COVID-19 in nonhospitalized individuals might differ. Finally, loss to follow-up may have introduced selection bias.

CONCLUSIONS

In this study, we observed the tpersistence of COVID-19-related symptoms. More specifically, 86% and 96% reported the presence of 1 or more symptoms at 6 and 12 weeks, respectively, after onset of COVID-19-related symptoms, as compared with prior hospitalization with COVID-19. The dominating symptoms were fatigue, dyspnea, cough, chemosensory dysfunction, and headache. Overall, there is an urgent need for well-designed longitudinal, multinational, and multisite studies. In such studies, a clear definition of inclusion criteria, uniform definitions of outcomes, and ways to measure these are necessary in order to continuously translate evidence of this new disease into the best possible interdisciplinary assessment and treatment for affected patients.

References

1. Coronavirus COVID-19 (2019-nCoV). Available at: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed 15 October 2020.
2. COVID-19 dashboard. Available at: https://experience.arcgis.com/experience/aa41b29149f24e20a4007a0c4e13db1d. Accessed 15 October 2020.
3. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. **2020**; 382:1708–20.
4. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:458–64.
5. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. **2020**; 288:335–344.
6. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA **2020**; 324:603–5.
7. Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with non-critical COVID-19 two months after symptoms' onset. Clin Microbiol Infect. **2021**; 27:258–63.
8. Fjaeldstad AW. Prolonged complaints of chemosensory loss after COVID-19. Dan Med J. **2020**; 67:A05200340.
9. Katzman R, Brown T, Fuld P, et al. Validation of a short orientation-memory-concentration test of congestive impairment. Am J Psychiatry **1983**; 140:734–9.
10. Medical Research Council. MRC Dyspnoea Scale/MRC Breathlessness Scale—research. Available at: https://mrc.ukri.org/research/facilities-and-resources-for-researchers/mrc-scales/mrc-dyspnoea-scale-mrc-breathlessness-scale/. Accessed 8 November 2020.
11. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
12. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. **2020**; 324:782–93.
13. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA **2020**; 323:2052–9.
14. Reilev M, Kristensen KB, Pottegård A, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol. **2020**; 49:1468–81.
15. Denova-Gutiérrez E, Lopez-Gatell H, Alomia-Zegarra JL, et al. The association between obesity, type 2 diabetes, and hypertension with severe COVID-19 on admission among Mexicans. Obesity. **2020**. doi:10.1002/oby.22946
16. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:993–8.
17. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol **2020**; 5:1265–73.
18. Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol **2021**; 6:116–8.
19. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine **2020**; 25:100463.
20. Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res **2020**; 21:163.
21. Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, et al. Neurotropism of SARS-CoV 2: mechanisms and manifestations. J Neurol Sci **2020**; 412:116824.
22. Desforges M, Le Coupanec A, Stodola JK, et al. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res **2014**; 194:145–58.
23. Zubair AS, McAlpine LS, Gardin T, et al. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. **2020**; 77:1018–27.
24. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. **2020**; 382:2268–70.
25. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. **2020**; 11:995–8.
26. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ **2020**; 371:m3862.
27. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet **2020**; 395:1417–8.
28. Bradley BT, Maioli H, Johnston R, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet **2020**; 396:320–32.

29. Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. **2020**; 5:1281–5.

30. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. **2020**; 383:120–8.

31. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. J Rehabil Med. **2020**; 52:jrm00063.

32. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA **2010**; 304:1787–94.

33. Richards M, Jarvis MJ, Thompson N, Wadsworth ME. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. Am J Public Health **2003**; 93:994–8.

34. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ **2020**; 369:m1966.

35. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect **2020**; 81:e4–6.

36. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol. **2021**; 93:1013–22.

37. Schmidt K, Worrack S, Von Korff M, et al; SMOOTH Study Group. Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: a randomized clinical trial. JAMA **2016**; 315:2703–11.