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THE 2019 CORONAVIRUS DISEASE EVOLUTION (COVID-19) SYMPTOMS IN THE FIRST TWELVE MONTHS OF THE ILLNESS

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Abstract

Background: There aren't much reliable long-term data on the symptoms of COVID-19 (coronavirus disease 2019). For up to a year from the start of the illness, we assessed the onset, severity, and recovery of symptoms over the whole range of disease severity.

Method:. Amsterdam, Netherlands-based RECoVERED Study is a prospective cohort study. Following a diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the local public health agency and hospitals, participants who were at least 18 years old were enlisted. Patients completed standardized symptom questionnaires at enrollment, one week and one month later, and then every month after that. In accordance with World Health Organization (WHO) guidelines, clinical severity was determined. Using Kaplan-Meier techniques, the length of time from the start of the disease to the resolution of symptoms was compared by clinical severity. We examined for factors that affect recovery time using multivariable Cox

Results. Between 11 May 2020 and 1 May 2021, 342 COVID-19 patients (192 [56%] male) were enrolled, of whom 99/342 (29%) had mild, 145/342 (42%) moderate, 56/342 (16%) severe, and 42/342 (12%) critical disease. The proportion of participants who reported at least 1 persistent symptom at 12 weeks after illness onset was greater in those with severe/critical disease (86.7% [95% confidence interval {CI} = 76.5–92.7%]) compared to those with mild or moderate disease (30.7% [95% CI = 21.1–40.9%] and63.8% [95% CI = 54.8–71.5%], respectively). At 12 months after illness onset, two-fifths of participants (40.7% [95% CI = 34.2–7.1])continued to report ≥1 symptom. Recovery was slower in female compared to male participants (adjusted hazard ratio [aHR] 0.65 [95% CI = .47–.92]) and those with a body mass index [BMI] ≥30kg/m2 compared to BMI <25kg/m2 (hazard ratio [HR] 0.62 [95%CI = .39–.97]).

Conclusions. A year after the start of the illness, COVID-19 symptoms persisted, even in some people with minor cases. The biggest predictors of the rate of symptom improvement were female sex and fat.

Keywords: symptoms, evolution, long-term COVID

Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has a clinical spectrum that spans from asymptomatic presentation to deadly illness. While there is a wealth of information regarding the acute symptomatology of hospitalized patients [1-4], there is a dearth of comprehensive longitudinal data regarding the development of long-term symptoms across the whole spectrum of COVID-19 severity. Furthermore, not much is known about the risk factors that could influence recovery and present a chance for therapy or intervention. According to observational studies, 4–12 months following the onset of symptoms, over half of hospitalized patients [5-7] and almost one-third of nonhospitalized patients [8] reported at least one persistent symptom.

Furthermore, anecdotal evidence about the effects of persistent post-COVID-19 symptoms on quality of life, day-to-day functioning, and mental health has been made available through online patient-led support groups [9]. In fact, both the economic productivity of society and the quality of life of an individual may be significantly harmed by post-COVID syndrome, also known as long-term COVID or post-acute sequelae of SARS-CoV-2 infection [PASC] [5, 10, 11].
A prospective cohort study of people living in the Amsterdam municipal region of the Netherlands who are infected with SARS-CoV-2 is called RECoVERED. In individuals with mild, moderate, severe, and critical COVID-19, we assessed the frequency, intensity, and duration of symptoms up to a year after the illness started. We also looked at baseline factors that influence how long it takes to recover from symptoms.

Method:

Study design and participants

An ongoing cohort study of COVID-19 patients in Amsterdam, the Netherlands, is called RECoVERED. The purpose of the study is to characterize the immunological, clinical, and psychological effects of infection with SARS-CoV-2. Registration opened on May 11, 2020. The Public Health Service of Amsterdam (PHSA) used notification data of laboratory-confirmed SARS-CoV-2 infections (by polymerase chain reaction [PCR] or validated antigen test [12]) to identify nonhospitalized individuals. Eligible patients were contacted by trained study staff over the phone within seven days of the SARS-CoV-2 diagnosis. Using admission data, prospective enrolled hospitalized participants were located and contacted on the COVID-19 wards of two academic hospitals in Amsterdam. Positive PCR results and/or SARS-CoV-2-specific serology (using the WANTAI SARS-CoV-2 Ab ELISA) were the diagnostic methods used in hospitals to diagnose COVID-19 cases. The latter method was used as an extra diagnostic tool for cases with high clinical suspicion of COVID-19 during times of extreme pressure on tertiary care. After being step-down from the intensive care unit (ICU), COVID-19 patients who had been admitted were enrolled. A restricted group of hospitalized patients who were infected during the “first wave” of COVID-19 in the Netherlands were contacted after discharge up to June 30, 2020, and within three months of the SARS-CoV-2 diagnosis. Recruitment is still underway, and by June 1, 2021, we included all individuals who had completed at least one month of follow-up in the current analysis.
The previously mentioned validated antigen test, serology, or prior laboratory confirmation of SARS-CoV-2 infection were among the eligibility requirements. Other requirements for inclusion were being between the ages of 16 and 85, living in the Amsterdam metropolitan area, and having a sufficient command of either Dutch or English. Those who were living in a nursing home before contracting SARS-CoV-2 were not included since they could not go on their own to follow-up appointments. People with mental illnesses that might make it difficult for them to follow study protocols were also disqualified. The Amsterdam University Medical Center’s medical ethical review board granted approval for the RECoVERED study (NL73759.018.20). Written informed permission was acquired by each subject.

Study procedure

Study visits were conducted on the hospital ward (if hospitalized) or at the participant's home (if nonhospitalized) on the day of enrollment (D0 study visit). One of the two research locations—Amsterdam University Medical Center [UMC] [location AMC] and PHSA—was visited again later. Every visit was carried out by medical study personnel with training.A symptom questionnaire on the existence, start and stop dates, and intensity of eighteen symptoms (based on the World Health Organization Case Report Form [14]) was filled out at the D0, D7, and D28 study visits (Supplementary Figure 2). Participants answered monthly online questionnaires about the presence of symptoms starting in the second month following enrollment.

Heart rate, oxygen saturation, and respiratory rate (RR) were obtained from hospital records for patients who were retrospectively included, or it was measured during the D0 and D7 study visits. During participant interviews, sociodemographic information as well as information on prior medical history, COVID-19-related problems, treatment, and investigations were gathered. Whenever accessible, computerized medical records were used to confirm self-reported data.

Definitions :

The first day of symptoms for COVID-19 patients was considered the illness onset; for asymptomatic patients, the SARS-CoV-2 diagnosis date was used. Full healing was characterized by the cessation of all COVID-19 symptoms. The acute phase of the disease was defined as the first four weeks following the commencement of the illness, and post-COVID syndrome as symptoms that persisted for at least twelve weeks following the onset of the illness, in accordance with National Institute for Health and Care Excellence (NICE) standards [15].

Clinical severity groups were established by physical measurements obtained from D0 and D7 study visits, in accordance with WHO COVID-19 disease severity guidelines [16]. A RR of less than 20 minutes and a SpO2 of more than 94% on room air were considered to be indicators of mild disease; an RR of 20–30 minutes and a SpO2 of 90–94% on room air (or receiving oxygen therapy, in the event that an off-oxygen measurement was unavailable) was considered an indicator of moderate disease; an RR of more than 30 minutes and a SpO2 of less than 90% on room air (or receiving oxygen therapy) was considered an indicator of severe disease; and a critical illness was any time an ICU admission was necessary due to COVID-19.

With the exception of dyspnea, which was assessed using the six-point modified Medical Research Council (mMRC) breathlessness scale [17], the severity of each symptom was graded on a four-point scale. The following conditions were present at the beginning of the illness and were identified by the WHO as being linked to severe COVID-19 [16]: diabetes mellitus (DM), liver disease, chronic kidney disease, chronic lung disease (CLD), cardiovascular disease (CVD), immunodeficiency, cancer, cerebrovascular disease, dementia, or mental illness. Because body mass ndex (BMI) was measured differently and classified in kg/m2 as follows: <25, underweight or normal weight; 25–30, overweight; and >30, obese, obesity was omitted from the comorbidity variable. The nation of birth of the research subject and their parents determined their ethnicity [18].Loss to follow-up (LTFU) was defined as two consecutive no-show visits after three attempts to make contact or as an active exit from the research. The last date of communication with the participant was used to determine the date of LTFU.

Statistical analysis :

Participants' clinical and sociodemographic traits were analyzed across clinical severity categories.The number of participants reporting each symptom since illness onset over the total number of participants in follow-up at that point was used to calculate the incidence proportions for 18 different symptoms (based on the WHO/ISARIC Case Report Forms [CRF] [14]) at 1, 4, and 12 weeks after illness onset. The results were compared by clinical severity group. Participants without symptoms added to the denominator. We limited this study to prospectively enrolled participants due to the possibility of recollection bias in reporting symptom start. Transition plots, stratified by

clinical severity group, were used to display changes in self-reported symptom severity over time during the acute phase for symptoms reported by more than 20% of participants 12 weeks following symptom onset.

Using information from both prospectively and retrospectively enrolled participants, Kaplan-Meier survival curves were used to determine the percentage of participants with continued symptoms (both overall and for each symptom individually). The at-risk period started at the onset of the illness and lasted until the recovery of the symptoms, the loss of follow-up, the date of the first vaccination (to eliminate any potential impact of vaccination on recovery time), or the last study visit before June 1, 2021 (i.e., the administrative censor date), whichever came first. All symptom survival analyses did not include asymptomatic subjects.

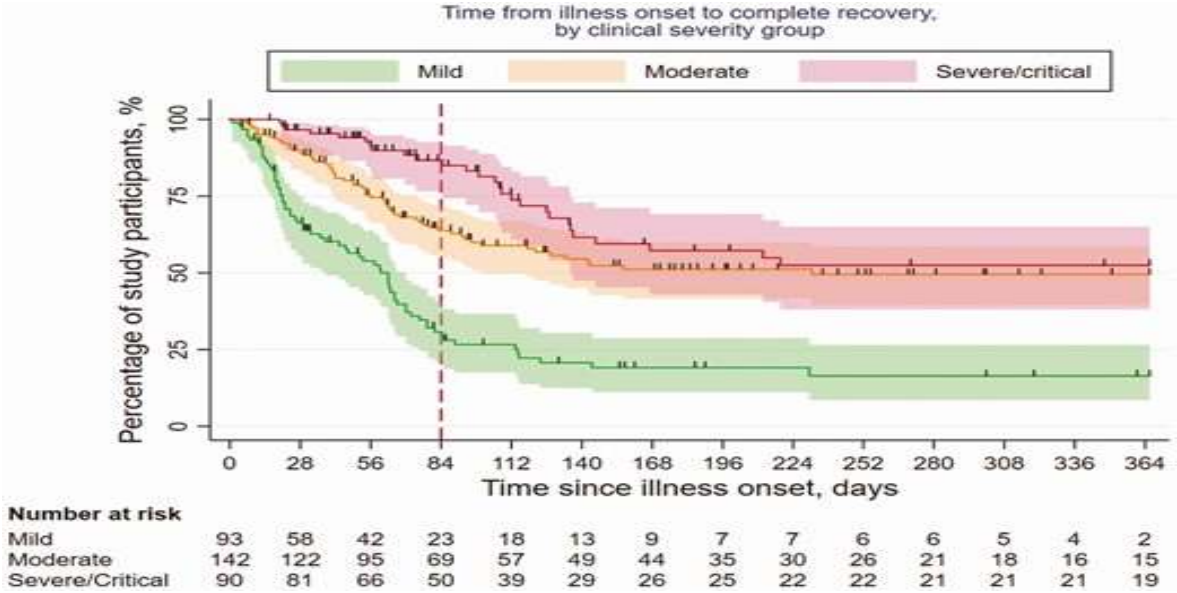
Supplementary Methods provides an analysis of the factors linked to the duration of symptom recovery. P <.05. was used as the threshold for statistical significance. R (RStudio, v.1.2.5033) and Stata (StataCorp, v.15.1) were used for statistical analyses

Results:

Study population

Supplementary Figure 1 summarizes participant enrollment and follow-up. 342 participants were enrolled between May 11, 2020, and May 1, 2021, the majority (251/343;73%) prospectively. Results shows that of these 342, 99 (29%) had mild disease, 145 (42%) moderate disease, 56 (16%) severe disease, and 42 (12%) critical disease. No participant was enrolled based only on the presence of SARS-CoV-2-specific antibodies; all had prior confirmation of SARS-CoV-2 infection by PCR or antigen testing at the time of enrollment.

Individuals with severe or critical disease had higher BMIs (P <.001), were older (P <.001), and were more likely to have been diagnosed with DM, CLD, or CVD (Table 1). The median interval between the onset of sickness and enrollment was 9 days (IQR = 5–14) for prospective enrollees and 85 days for those who were not.



342 participants were enrolled between May 11, 2020, and May 1, 2021, the majority (251/343;73%) prospectively. Results shows that of these 342, 99 (29%) had mild disease, 145 (42%) moderate disease, 56 (16%) severe disease, and 42 (12%) critical disease. No participant was enrolled based only on the presence of SARS-CoV-2-specific antibodies; all had prior confirmation of SARS-CoV-2 infection by PCR or antigen testing at the time of enrollment.Individuals with severe or critical disease had higher BMIs (P <.001), were older (P <.001), and were more likely to have been diagnosed with DM, CLD, or CVD (Table 1).

The mean duration from the onset of sickness and enrollment was 9 days (IQR = 5–14) for participants who were enrolled prospectively, and 85 days (IQR = 72–94) for those who were enrolled retrospectively. Sixty-six individuals were lost to follow-up as of June 1, 2021. Two deaths happened during follow-up, and both were caused by COVID-19.

Incidence Proportions and Severity of Symptoms During the Acute Phase of Infection

The two most commonly reported symptoms overall were fatigue and cough, and there was no difference in their incidence proportion during the acute period across the clinical severity groups .During the acute phase of the disease, the incidence proportions of headache, diarrhea, and dyspnea were considerably higher in patients with severe/critical illness than in patients with mild or moderate illness; the opposite was true for fever, sore throat, lack of appetite, and rhinorrhea.

Transition plots revealed that while the majority of participants moved from the more persistent symptoms (fatigue, dyspnea, loss of taste and/or smell, and myalgia) to a lower level of severity over time, some moved to a greater level of severity Time Needed for Symptom Recovery Compared to individuals with mild COVID-19, symptomatic participants with moderate and severe/critical disease required a considerably longer time to recover (Figure 1).Twelve weeks after the start of the illness, 30.7% (95% CI = 21.1%–40.9%) of participants with mild disease, 63.8% (95% CI = 54.8–71.5%) with moderate disease, and 86.7% (95% CI = 76.5–92.7%) with severe/critical disease reported at least one persistent symptom, matching NICE criteria for post-COVID syndrome.

The median recovery period for those with mild disease was 63 days (Figure 1), although at 12 months following the commencement of the illness, 16.4% (95% CI = 8.5–26.5%) of them were still reporting at least one symptom. The average recovery period for patients with moderate disease was 232 days (7.6 months), and 12 months from the start of the illness, 49.5% of patients (95% CI = 39.6–58.6%) were still reporting at least one symptom. At least one continuing symptom was reported by more than half of patients with severe/critical illness twelve months after the illness started (52.5% [95% CI = 38.0–65.1%]). Kaplan-Meier estimates for each of the 18 symptoms are displayed in Supplementary Figure 4a–4e, categorized by clinical severity group. Individuals who received vaccinations while still experiencing symptoms (n = 91; median interval between symptom onset and vaccination) 249 days were right-censored at date of first vaccination.

What Determines How Long It Takes to Get Rid of Symptoms

The adjusted hazard ratio (aHR) of 0.65 (95% CI =.47–.92) indicates that female participants recovered 35% more slowly than male participants. Furthermore, obese people recovered 38% slower than normal-weight participants after controlling for comorbidities, age, and sex (aHR 0.62 [95% CI =.39–.97]). Every covariate in the model satisfied the proportional risks assumption.

This suggests that enrolling retrospectively enrolled individuals with more severe/critical condition and greater BMI greatly influenced estimations of recovery time. The effect of BMI was minimized when the study was limited to prospectively enrolled people.

The results indicate that a delayed recovery from loss of smell and/or taste was associated with obesity at the outset of illness (aHR 0.51, 95% CI =.32–.82). Age was linked to a shorter rate of recovery from myalgia (aHR 0.78, 95% CI =.68–.89) and dyspnea (aHR 0.80, 95% CI =.69–.93). Recovery from fatigue was substantially correlated with the number of comorbidities at the beginning of the illness; those with one comorbidity recovered twice as slowly as those without comorbidities (aHR 0.51, 95% CI =.34–.76). No statistically significant effect on time to diagnosis was observed when we substituted the total number of comorbidities with the presence of each of CVD, CLD, or DM in the multivariable models for each of these symptoms.

Discussion

This study, to the best of our knowledge, is among the first to present comprehensive longitudinal data on the progression of COVID-19 symptoms in a group of patients with mild to critical illness up to a year following the commencement of the illness. Though the most persistent COVID-19 symptoms during the acute phase of the disease improved overall, over four-fifths of patients with

severe/critical disease, nearly two-thirds of the moderate group, and approximately one-third of the mild group met the NICE criteria for post-COVID syndrome.

One in six individuals with mild disease and around half of those with moderate or severe/critical disease reported having at least one lingering symptom even a year after the illness started. Obesity at the beginning of the illness and female sex were significant factors in the delayed symptom improvement.
The main objective has been to prevent hospitalization and fatality as soon as possible since the COVID-19 outbreak began. Consequently, the long-term effects of COVID-19 have not gotten much attention, particularly from patients who are not hospitalized. Twelve weeks after the start of the illness, up to one-third of the people in our research who had mild COVID-19 still reported symptoms.

In fact, our cohort's overall percentage of participants (60.2%) who met the NICE definition of post-COVID syndrome was greater than estimates from the UK Office for National Statistics and among healthcare workers [20, 21], although it was nevertheless similar to earlier prospective cohort studies [7, 8, 19]. The fact that our analysis was restricted to individuals who exhibited symptoms may account for some of this, but the implications of these proportions on a worldwide scale are probably significant. Thus, it is evident that immediate action is needed to address this developing public health emergency.

Despite the fact that patient advocacy groups have played a significant role in elevating post-COVID syndrome research to a priority [22], it is challenging to compile all of the available data because studies to date have varied in terms of study population, follow-up duration, and symptoms assessed [15].
Furthermore, a variety of symptom patterns are included in the post-COVID syndrome category [23], which leads to a heterogeneous patient group in need of various therapy approaches. Establishing a consensus-driven, empirically supported definition of post-COVID syndrome is essential for cross-study and cross-setting comparisons as well as for the creation of syndrome-specific therapies. For instance, our research indicates that healing after the sickness has lasted more than six months is not typical, indicating that those who continue to have symptoms after this time may need more extensive assistance and care.
Furthermore, independent of age or the number of comorbidities at the outset of illness, our results imply that women and obese people may benefit from early intervention. Apart from the immediate impact of obesity on recuperation, a high body mass index (BMI) is linked to a poorer socio-economic position and limited availability of health and care services [24], which could potentially exacerbate a delayed symptom resolution. Therefore, lowering the incidence of obesity may aid in lowering COVID-19's long-term consequences as well as its acute problems [4, 25].
The most often reported symptom, even in those with mild or moderate disease, was fatigue, both during the acute phase and 12 weeks after the start of the illness. According to earlier estimates, weariness can have a large social impact because it can lead to direct medical expenses as well as indirect financial losses from lower economic productivity [26]. Since the majority of COVID-19 occurrences globally are mild cases, it is important to prioritize the development of methods for preventing, diagnosing, and treating post-COVID tiredness. Additionally, a significant number of patients with moderate and severe/critical condition also experienced dyspnea and myalgia for longer than 12 weeks. Comparable outcomes have been documented in several contexts: Six months after the illness began, previously-hospitalized COVID-19 patients in Wuhan, China, continued to exhibit aberrant chest imaging findings and pulmonary diffusing capacity [5], while a cross-sectional investigation of hospitalized COVID-19 patients in the UK found that the most participants in a cross-sectional study of hospitalized COVID-19 patients in the UK reported myalgia at a median follow-up of 16 weeks following hospital discharge [27]. According to our multivariable analysis, the most significant factor associated with a slower rate of recovery from

each of these symptoms was older age. Investigating the fundamental cause of these symptoms' persistence in elderly individuals may aid in the discovery of therapies that could be helpful in their recuperation.[28,29]

The study analyzed the natural progression of COVID-19 symptoms using frequent symptom questionnaires collected since illness onset. It included patients with mild and critically ill patients, allowing for a comprehensive representation of the disease spectrum. However, limitations included the lack of language options, underrepresentation of individuals with a migration background, and the potential for the progression of disease to not be representative for patients infected with other variants. The study also found that post-COVID syndrome is common, even after mild disease, with symptoms persisting for twelve months. The study suggests that creating an environment conducive to healthy living behaviors is crucial during a pandemic.[30]

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