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Results of a thematic analysis to explore patients' experiences with long COVID-19: a conceptual model of symptoms and impacts on daily lives

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Short title: The patient experience with long COVID: a conceptual model

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Abstract

Objectives: There has been limited qualitative research on patients' experiences with long coronavirus disease 2019 (COVID-19), and how specific symptoms impact their daily lives. The study objectives were to understand the patients' lived experience of long COVID-19, and to develop a conceptual model to represent the symptoms and their impact on overall quality of life.

Setting: Qualitative study consisting of a literature review, and in-depth clinician and patient semi-structured interviews.

Participants: Forty-one adult patients with long COVID-19, of whom 18 (44%) were recruited through Regeneron Pharmaceuticals Inc.'s clinical trials and 23 (56%) through recruitment agencies; 85.4% were female and 73.2% were White. Five independent clinicians treating patients with long COVID-19 were interviewed.

Primary and secondary outcomes: Interview transcripts were analysed thematically to identify concepts of interest spontaneously mentioned by patients, including symptoms and their impacts on daily life, to guide development of the conceptual model.

Results: Findings from the literature review and clinician and patient interviews resulted in the development of a conceptual model comprising two overarching domains: symptoms (upper respiratory tract, lower respiratory tract, smell and taste, systemic, gastrointestinal, neuro-cognitive and other) and impacts (activities of daily living, instrumental activities of daily living, physical impacts, emotional, social/leisure activities and professional impacts). The symptoms reported were heterogenic; neuro-cognitive

symptoms, such as numbness, ringing in ears, haziness, confusion, forgetfulness/memory problems, brain fog, concentration, difficulties finding the right word, and challenges with fine motor skills, were particularly pertinent for several months.

Conclusion: This study revealed empirical insights directly from patients with long COVID-19. The conceptual model, developed based on patient experience data, highlighted numerous symptoms including neurocognitive symptoms that ultimately impact patients' physical and mental wellbeing, and suggest humanistic unmet needs. Prospective real-world studies are warranted to understand the pattern of long COVID-19 experienced in larger samples over longer periods of time.

Word count: 300/300 words

Strengths and limitations of this study (up to five bullet points)

- This study included a comprehensive literature review alongside in-depth, qualitative interviews with patients recruited from both clinical trials and healthcare research firms, as well as independent clinicians, in order to provide rich empirical insights into the under-researched patient experience of long coronavirus disease 2019 (COVID-19).
- While knowledge about acute COVID-19 symptoms and patient experience is relatively comprehensive, to our knowledge this qualitative study is the first to provide specific and crucial insights from the patient perspective into the symptom experience of long COVID-19 and its long-term impacts on daily life, including neurocognitive, physical and emotional functioning.
- A limitation of this study was that participants were predominantly White and female so additional research is warranted to further explore the impact of long COVID-19 in more diverse groups.

Introduction

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), can experience long-term effects even if the virus is no longer detected with standard methods [1]. These effects are often referred to as “long COVID”, “post-COVID-19 syndrome” or “post-acute sequelae of SARS-CoV-2” [2-4], and definition may vary. According to the Centers for Disease Control and Prevention (CDC), patients with long COVID-19 continue to experience symptoms for ≥4 weeks after the initial infection with SARS-CoV-2 [1]. The National Institute for Health Excellence (NICE) uses the term “post-COVID-19 syndrome” and defines it as “*signs and symptoms that develop during or after an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis”* [5]. While the World Health Organization (WHO) defines the condition as *“the illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within 3 months from the onset of COVID-19, with symptoms and effects that last for at least 2 months.”* Similar to the NICE guidelines, the WHO specifies that *“the symptoms and effects of post COVID-19 condition cannot be explained by an alternative diagnosis”* [6].

The most commonly reported symptoms of long COVID-19 in current literature are fatigue, chest pain, muscle aches, persistent cough, fever, shortness of breath or difficulty breathing, loss of smell or taste, depression or anxiety, trouble speaking, and memory, concentration or sleep problems [1, 6-10]. The CDC and NICE have indicated that long COVID-19 can affect anyone who has been infected, regardless of the severity of the initial infection [1, 5]. However, risk factors for long COVID-19 have been reported

to include female sex, older age and a history of more than five symptoms during the infection [11, 12]. Specific features of long COVID-19 have been identified via immune profiling, and include elevated humoral responses against SARS-CoV-2, and decreased levels of cortisol [13]. The reported prevalence of long COVID-19 ranges considerably, from 8 to 57% depending on the source and patient population evaluated [1, 14, 15]. While the exact prevalence of long COVID-19 is unclear, it is evident that management of patients with the disease poses a potentially significant burden for healthcare systems globally [16]. The health and economic consequences of long COVID-19 are predicted to be in line with acute disease; when calculating for a reduced quality-adjusted life expectancy, long COVID-19 has been estimated to cost around $2.6 trillion in the USA [17, 18].

Although COVID-19 is a global public health issue, and there is an increasing body of clinical and epidemiological literature on the incidence and prevalence of symptoms, to date there has been little empirical evidence directly from patients regarding the symptoms associated with long COVID-19 and how these symptoms impact their lives [7, 19-22]. Previously, we reported that the manifestation of symptoms in patients who were diagnosed with COVID-19 was heterogeneous and significantly affected all aspects of patients' lives; however, the study focused on patients with acute disease [23]. Due to its discrete characteristics, it is essential to understand and study long COVID-19 separately from acute COVID-19. We therefore sought to: (i) gain an in-depth understanding of the patient experience of long COVID-19 symptoms and the impact on their daily lives; and (ii) understand the patient experience within the

framework of a conceptual model based on empirical patient-relevant evidence informed by literature and patient and clinician interviews.

Methods

Literature review

Search strategy

An electronic search was performed using PubMed to identify qualitative papers exploring the patient experience of long COVID-19 in the last 10 years. A combination of search terms related to the target population were used, including (**Table S1**): post-acute sequelae of SARS-CoV-2 infection, long COVID-19, and patient experience (eg, symptoms, impacts). The search was limited to humans and English language publications. During the first stage of screening, articles were reviewed by title and abstract only. The second screening stage included full-text review of articles that were retained after the first screening (**Figure 1**). Articles that did not report on long COVID-19 disease and its experienced symptoms or impacts were excluded.

Qualitative in-depth interviews with patients and clinicians

Patients

A purposive sample of patients was initially identified through Regeneron Pharmaceuticals Inc.'s clinical trial programme (COV-2066 in hospitalised participants [NCT04426695] and COV-2067 in non-hospitalised participants [NCT04425629]) [24, 25]. This patient sample was extended to the real-world through two independent healthcare research firms, Rare Patient Voice and PRC Corporation, which specialise in the recruitment of difficult-to-reach populations (**Supplementary Methods)**. Adults (aged ≥18 years) with a positive SARS-CoV-2 polymerase chain reaction test ≥180

days prior to enrolment into this study, experiencing long COVID-19 symptom(s) that could not be explained by an alternative diagnosis, and who were willing and able to participate in one 60-minute audio-recorded telephone or online interview in English, were included in the study. Full inclusion and exclusion criteria are provided in the **Supplementary Methods**.

Patients' demographic information, including age, weight, height, sex, ethnicity, race, education level, employment status, occupation, living situation, marital status and household income, were collected. Comprehensive health information was also collected, including general health status at the time of interview, time since the beginning of COVID-19 symptoms, any hospitalisation due to COVID-19 and time since hospitalisation, smoking status, existing chronic disease or conditions, treatment with a monoclonal antibody, and COVID-19 vaccination status (**Table 1**).

Clinicians

Clinicians were eligible to participate if they were regularly seeing/treating more than five patients a week with long COVID-19 in the USA, and were willing to participate in a 60-minute audio-recorded telephone interview in English. Clinicians who only treated patients who resided in an institutional setting (eg, nursing home) were excluded. There were no pre-defined sample quotas set for the five clinicians; however, the recruitment process sought a diverse representation of professions (eg, general practitioners, nurses), specialties, and treatment settings (eg, hospital/non-hospital settings) where patients with long COVID-19 were regularly treated. A heterogeneous sample of five clinicians, who served as research consultants, was considered sufficient to obtain insights for input into the conceptual model.

Sampling

A purposive sampling approach was used and initially defined to target patients who were enrolled in Regeneron Pharmaceuticals Inc.'s clinical trials in the long COVID-19 sub-study in the USA. Additional recruitment of patients from external recruitment agencies were matched to the trial patients according to inclusion criteria. Due to the heterogeneity of both long COVID-19 symptoms and the affected population [26], sampling covered a target population experiencing a range of symptoms. This ensured a diverse sample of up to 50 patients, which was estimated as an adequate sample size to reach conceptual saturation in the concepts of interest (COIs) [27, 28]. The sample size was anticipated to be adjusted downward based on recruitment feasibility and saturation analysis. In qualitative research, whether the sample size to obtain probable symptoms and impacts from a population is substantial or not is usually defined by the principle of data saturation (see below) [29]. The final sample size was to be determined by saturation based on good research practice [27, 30] and requirements by the US Food and Drug Administration for establishing content validity [31].

Patient and clinician interviews

Patient interviews were conducted via Microsoft Teams by four experienced qualitative researchers who received specific training for this study, and who had backgrounds in psychology and anthropology as well as ≥2 years' experience in qualitative research. Patients were asked open-ended questions to provide spontaneous inputs regarding the symptoms of long COVID-19 and the impacts these had on their daily lives. Specific questions on reported symptoms were also asked, which included a description of the symptom, as well as improvement or worsening, changes over time, and total duration,

severity and resolution of symptoms. Emotional impacts, social interactions and disruption to day-to-day activities were also explored.

Clinician interviews were also conducted by experienced qualitative researchers via telephone. During the interview process, clinicians provided insights into patients' experiences of long COVID-19. All relevant findings extracted from the articles in the conceptual literature review and the clinician interviews were organised into a conceptual model to detail all potential COIs that could inform the patient experience of long COVID-19.

Ethical approval

All study documents (the protocol, interview guides, demographic and health information form, screener form and informed consent form) were approved by the Western Institutional Review Board-Copernicus Group Independent Review Board (IRB) before study initiation (IRB tracking # 20214272). Electronic informed consent was obtained from all patients. Patients were paid a fee in line with fair market value to cover the time taken to participate in the study.

Thematic data analysis

All interviews were audio recorded and transcribed verbatim. Transcripts from patient interviews were analysed thematically [32], using detailed line-by-line open and inductive coding [33-35] within ATLAS.ti software (Scientific Software Development GmbH). Coding was tailored to the research objectives of the study, which were the identification of symptoms and impacts of long COVID-19, including those spontaneously mentioned by patients as well as further probing of COIs. Codes and

quotations were compared with the rest of the data and inductively categorised into higher-order overarching categories referred to as concepts, sub-domains and domains, reflecting their conceptual content underpinning.

Saturation analysis

Saturation refers to data adequacy, ie, the point at which no new relevant information emerges from additional qualitative data [27, 28, 36]. Within patient-reported outcomes research, saturation has been defined as "*the point in the data collection process when no new concept-relevant information is being elicited from individual interviews or focus groups, or no new information is deemed missing during cognitive interviewing*" [29]. In the present study, the adequacy of the sample size was evaluated by a saturation analysis. Saturation analysis was conducted by grouping interviews chronologically and comparing the emerging sub-domains that reflected the conceptual categorisation of the codes. The sub-domains that emerged from the second quintile were compared with the sub-domains that emerged in the transcripts from the first. This comparison was repeated for each additional quintile. The cycle of data collection and analysis was continued until additional data collection produced no or minimal new information to further confirm or challenge the conceptual model.

Conceptual model

A conceptual model identifies and characterises COIs related to a health condition [37]. To develop a conceptual model of patient experiences with long COVID-19, data extracted from identified articles were inductively categorised into higher-order conceptual domains. Once coding was complete, a preliminary conceptual model was

developed using the concepts extracted from PubMed; this was then revised with clinician input and further refined based on the results from patient interviews. Each concept was then considered and grouped into higher-order domains. If a concept was repeated across multiple sources, it was listed once. Ultimately, standard analytical techniques of conceptual model development were used to develop a visual representation of how the COIs relate to each other, grounded in a data-driven process based on patient-relevant empirical evidence [33-35, 38].

Analysis

SAS software version 9.4 (SAS Institute, USA) was used for descriptive analysis. Continuous variables were described by their frequency, mean, standard deviation, median, first and third quartiles, extreme values (minimum and maximum values), and the number of missing values. Categorical variables were described by the frequency and percentage of each response choice, with missing data included in the calculation of the percentage.

Results

Literature review findings

The PubMed search of qualitative studies identified 115 abstracts for screening: 95 articles were excluded after abstract review and 20 full-text articles related to symptom and impact concepts were included in the final literature analysis (**Figure 1**). Articles presented symptoms at different conceptual levels (domain, sub-domains and concepts). Impacts were also presented at a high level of abstraction, eg, worsened quality of life.

Patient demographics and interviews

Interviews were conducted between 30 September 2021, and 12 May 2022. The study included 41 patients, of whom 18 (44%) were recruited through clinical trials and 23 (56%) through recruitment agencies (**Table 1**). The mean age was 53.6 years, 85% were female and 73% were White. The mean time between the start of any COVID-19 symptoms and the interview was 12 months (range: 1–25 months). Twenty-two patients (54%) received two doses of either the Moderna (27%) or the Pfizer/BioNTech (27%) vaccine, and 49% had been hospitalised. Most patients reported good (34%) or fair (37%) general health. At the time of the interview, hypertension/high blood pressure, arthritis, asthma, diabetes and mood disorders were self-reported by 18 (44%), 16 (39%), 10 (24%), nine (22%) and seven (17%) patients, respectively.

Clinician interviews

Participating clinicians included nurses and physicians who treated between 10 and 40 patients a week for COVID-19 (**Table 2**). All clinicians considered the CDC [1], WHO

[6] and NICE [5] guidelines (of ≥4 weeks after initially experiencing COVID-19 symptoms that cannot be explained by another condition) as the most appropriate timepoint for describing symptoms of long COVID-19, reasoning that they expected symptoms like cough to typically resolve after the acute phase of COVID-19 within this time frame.

Clinicians described fatigue, shortness of breath, chest pain/discomfort, cough, and loss of smell and taste as the most common symptoms experienced by patients with long COVID-19. In addition, they emphasised that long COVID-19 may affect any system of the body and that there was a wide variety of other, less common symptoms, such as headache, dizziness and hair loss. One clinician highlighted that many patients received a combination of treatments in relation to their symptoms, and that it became challenging to distinguish between less common symptoms related to long COVID-19 and the side effects of these treatments.

Clinicians reported that cognitive impairment accompanied common and less common symptoms, highlighting several mental health components such as depression, anxiety and feeling vulnerable. Additional impacts on quality of life included loss of appetite, sleep interruptions, lack of physical activity, inability to work and inability to perform activities of daily living (ADLs). Clinicians noted that most patients presented with ongoing symptoms from their initial COVID-19 diagnosis; of these, some presented cyclically. They also reported that a small number of patients who presented with severe respiratory symptoms were hospitalised, but most received care in outpatient settings. Clinicians suggested that most symptoms would eventually resolve, though they found it challenging to say exactly when this would happen.

Conceptual model development and saturation

Data from the literature review and clinician/patient interviews yielded two overarching domains: symptoms and impacts. The refined conceptual model is presented in **Figure 2**. Information was added in the conceptual model about the source of concepts included (literature review, clinician interviews and/or patient interviews). All patient-reported concepts included in the model were reported by at least two patients.

Of the 41 symptoms presented, 93% were identified in the first 24 interviews (**Table S2**). In the remaining group of nine interviews, only two additional sub-domains were identified: challenges with fine motor skills, and stiffness. Stiffness added granularity to the body aches/pain sub-domain previously identified and, with the highly heterogeneous nature of long COVID-19, we can expect that additional symptoms would emerge with additional interviews. This indicated that the current analysis was comprehensive regarding the key symptom domains. For sub-domains in the impact domain, all unique sub-domains (n=22) were identified in the first three groups of the saturation analysis (**Table S3**). No new impacts emerged in the final 16 interviews. This indicated that saturation was achieved for the reported impacts.

Symptoms

Symptoms experienced after the first 4 weeks of acute COVID-19, as reported by patients, were elicited during patient interviews. Symptoms were grouped into seven domains: upper respiratory tract, lower respiratory tract, smell and taste, systemic, gastrointestinal, neurocognitive, and other. Due to the variation and complexity of symptoms experienced, the domains extended across specific areas of the body (ie,

upper respiratory tract) to more general subdomains (ie, weakness or aches in the systemic domain, not exclusive or specific to one area of the body).

The upper respiratory tract domain reflected issues related to the sinuses and throat, and included symptoms such as phlegm, runny nose and sneezing, difficulty swallowing, and dry mouth. Difficulty in swallowing was described by one patient as like choking.

"I would choke on it like a bread, cracker, peanut butter, anything – pudding even, pudding would get stuck. Anything that's thick it didn't go down easy. If it was liquidy [stet] I got it to go down. Oatmeal would get stuck. Just like it was stuck there, and I'd be choking on it." **(Female, 50–59)**

The lower respiratory tract domain reflected issues related to the airways and lungs, and the sub-domains reflected symptoms such as shortness of breath, cough (including dry cough), difficulty breathing and chest pain.

"So the coughing was... it felt the same as COVID. It was a dry cough. I couldn't stop. It'd be like cough and I'd try to talk and here I'd start coughing again." **(Female, 40–49)**

Loss of smell and taste was a commonly reported symptom in patients with long COVID-19. The severity of loss of senses varied widely, with some patients describing a total loss, while others reported that their senses were altered.

"Now the coffee to me is very sour and I have to use 4–5 sugars for that sourness in my taste buds to go away. I never had a sweet tooth but the coffee itself it tastes burnt to me, I can't have it black like I used to." **(Female, 40–49)**

The systemic domain included various symptoms which affected the entire body, rather than a single organ or body part, such as fatigue, weakness, heart palpitations, body aches, joint pain, fever, stiffness and chills. Fatigue was specifically described by patients in terms of its severity, whether it improved or not, and how variable the fatigue was.

"Like, I literally could sleep all day and just lay there preferably sleeping. It just feels like I weigh 1000 pounds. I have no care for the things that need to get done. I don't care to eat; I don't care to work. I don't care... It's just a malaise, tiredness, and heaviness." **(Female, 50–59)**

The gastrointestinal symptoms reported were nausea, diarrhoea vomiting, and other stomach-related issues.

"I am having issues with digestion, appetite loss, I will have food that doesn't get digested well and just goes right through. Or I will have... issues with constipation so that's varying." **(Female, 30–39)**

Many patients experienced neurocognitive symptoms such as brain fog, dizziness, memory problems, difficulties finding the right word, and challenges with fine motor skills. Brain fog reflected the challenges patients experienced to focus and stay on task. Neurocognitive symptoms were particularly pertinent for extended periods of times, with some patients reporting symptoms for several months.

"A fog comes over you and you can't think what you're trying to say. It's just hard to explain. It's a very weird feeling. You're sitting there speaking and all of a sudden you

can't comprehend or concentrate to find the right words when you're trying to speak." (**Female, 50–59**)

"Very much so, I am dizzy a lot. Just going up and down the stairs. I live on the second floor. I have to hang onto the railing to make sure I am not going to fall. I have to concentrate on walking down the stairs. I have to concentrate on anything that I do that requires movement from me." **(Female, 50–59)**

"I've had a few severe situations with my memory. For instance, when I first started experiencing it, it's horrible that you're used to going and just driving, simple driving and knowing your way. For me being close to home and still forgetting how to get home, not retaining that, because I am kind of new to the area but still it shouldn't have been an issue." (**Female, 30–39**)

"I have trouble finding words. I know the words but I can't get them out. I'll have to, my family they're used to me now but I describe stuff because I can't think of the words." (**Female, 50–59**)

"Grabbing things and making sure I have a hold of them properly, otherwise I might not really be holding it… So I'll be smoking a cigarette and I'll go to take a puff of the cigarette and be like where did the cigarette go and it's fallen out of my hand and I didn't even know it." (**Female, 50–59**)

Impact on daily life

The overarching domain "impacts" is defined by the activities and health-related quality of life experiences that patients report have been affected because of having long

COVID-19. “Impacts” covered six sub-domains related to ADLs, instrumental activities of daily living (IADLs), physical impacts, emotional, social/leisure activities and professional impacts.

Quotations were categorized into ADLs if they referred to activities related to eating, drinking, getting up from a bed or chair, climbing stairs, and routines of self-care (eg, bathing).

“With the lack of energy, the fatigue, the shortness of breath when I am active, simply daily hygiene tasks. It’s physically exhausting to take a shower, so I do wash with soap and water and wash the important parts. I feel gross taking a shower because I am just too exhausted to do it.” **(Female, 50–59)**

IADLs included activities related to household chores, taking care of children or pets, shopping and meal preparation.

“I would say pretty much 90% of my meals have all been take-out since COVID. I’ve hardly cooked anything just because it’s been so difficult.” **(Female, 40–49)**

The physical impacts domain included sub-domains related to concepts associated with physical changes, such as changes to appetite and weight loss, hair loss and sleep disruption. It also included impacts on the ability to perform physical tasks such as walking and exercising.

“So it’s more of a you go to sleep and you wake up just as tired as when you were asleep. It can be really hard to wake up in the morning, really hard to get my brain functional in the morning, especially if it’s earlier.” (**Female, 30–39)**

The emotional domain included sub-domains associated with changes in the patient's psyche and mood in general, including issues associated with various worries and anxieties of having long COVID-19, depression, irritability, frustration, heightened emotional responses and not recognising oneself any longer.

"It's hard to put a label on it because it's almost like a loss of sense of self. That's the best way I can put it into words. It's overwhelming, like feeling of loss and depression where it's not getting any better. Before, I had depression level come and go and now it's just staying with me." **(Female, 50–59)**

Activities related to social life, hobbies and leisure activities as well as sports and exercise were categorised under social and leisure activities.

"So things like I used to... be very active in my church. I used to go every week multiple times, different events. I used to go out and hang out with friends. And those are things that I can no longer do. Not because of risk of catching COVID or something like that. But just because I physically don't have the ability." **(Female, 30–39)**

The professional domain captured changes in the patient's ability to work.

"And like I said my job, I was going to attempt to work from home but my supervisor tells me oh everyone is back in the office now. I am not ready to get dressed in office clothes and drive to work and be on time. My extra income is just not... there. And it's hard. I've tried to find jobs that I can when I feel okay, but nobody is trying to do that." **(Female, 50–59)**

Discussion

There is limited information on the patient experience of living with long COVID-19, and to our knowledge there is no current conceptual model that provides a visual representation of the symptoms and impacts of the disease. This qualitative study provides novel insight into the conceptualisation of the patient experience of long COVID-19. These rich patient qualitative insights are a useful resource to guide support and treatment requirements of those with long COVID-19 [39].

Following in-depth patient and physician interviews, we summarised the data captured in a simple and clinically grounded conceptual model comprising upper and lower respiratory symptoms, systemic symptoms, gastrointestinal symptoms, neuro-cognitive symptoms, altered or loss of smell and taste, and other symptoms. These symptoms were consistent with those reported by national and international health bodies such as the CDC [1], WHO [6] and NICE [5], and by systematic reviews [26, 40]. In addition to headache, dizziness and lightheadedness, which were also identified in the acute COVID-19 conceptual model [23], the long COVID-19 conceptual model included various neurocognitive symptoms such as numbness, ringing in ears, haziness, confusion, forgetfulness/memory problems, brain fog, concentration, difficulties finding the right word, and challenges with fine motor skills, and some of these symptoms were reported to be experienced for several months. Furthermore, while emotional concepts such as anxiety, depression, irritability and frustration were presented in the acute COVID-19 conceptual model [23], in the patients with long COVID-19 additional concepts included fear of reinfection, heightened emotional responses, indifference, not recognising oneself, and post-traumatic stress. At the time

our study was initiated, no other instruments were available to assess the impact of long COVID-19. Subsequently several instruments are now available. The modified COVID-19 Yorkshire Rehabilitation Scale, Symptom Burden Questionnaire for Long Covid, and post-acute (long) COVID-19 quality of life instrument each assess symptom burden in long COVID-19, but are not comprehensive in all symptoms identified in our model; particularly neurocognitive symptoms [41-43]. However, a handful of qualitative studies have demonstrated that patients with long COVID-19 report a very low state of mind and felt that their self-identity was affected, findings that are consistent with our own [20, 44]. Neuro-rehabilitation programmes for patients with long COVID-19 have proved helpful to improve working memory, verbal fluency and anxious-depressive symptomatology [45]. Our study further highlights the importance of understanding the impact these neurocognitive symptoms, which are not often reported during acute disease, can have on patients' emotional, social and professional lives.

In addition to symptoms, we also captured the impact of long COVID-19 and the changes in the daily lives of affected patients. The range of impacts due to long COVID-19 was consistent with those experienced during acute disease [23]; however, this study highlighted the emphasis on longer-term impacts. As the impacts of daily living occurred simultaneously with symptoms, one might infer that by reducing symptoms and/or their severity there might in turn also be a reduction of some, if not all, impacts. Studies in populations with acute COVID-19 have shown that improvements in symptoms are correlated with improvements in outcomes and patient quality of life. However, additional qualitative and quantitative research is required to address this

current knowledge gap, and further explore how management of symptoms in long COVID-19 could improve patients' lives.

Our study has two main limitations. First, the patients who were recruited from the external healthcare research firms closely matched the inclusion and exclusion criteria from the clinical trials. This approach may have resulted in a missed profile of patients with long COVID-19 who may be experiencing symptoms differently. Additional interviews with a broader exclusion and inclusion criteria could be considered as future research to determine whether they experience symptoms differently. Second, most of the patients in the present study were female and White. Nevertheless, this is consistent with other studies where the persistence of long COVID-19 symptoms for ≥12 weeks was higher in females than males [46]. There have also been reports on differences in prevalence of long COVID-19 symptoms in different ethnicities. One study that utilised data from community-based samples (>600,000) reported that an Asian population had a lower risk of persistent symptoms compared to a White population [46]. However, in other studies, Black Afro-Caribbean ethnic groups and other minority ethnic groups (native American, Middle Eastern or Polynesian) had a higher risk of long COVID-19 compared to a White population [12]. Additional studies are needed in different ethnic groups to fully understand the presentation and impact of long COVID-19 in different populations.

The present qualitative study provides unique and valuable insights on symptoms in patients with confirmed diagnoses of long COVID-19 and how it impacts their daily lives, including physical, emotional and psychological functioning. Improving our understanding of the patient experience of the disease will help healthcare providers

make informed decisions on optimised treatment options and the support needed for patients to improve their overall health-related quality of life, while also easing the burden on patient's families and society [44]. Although no obvious symptomatic profiles were found during the interviews with patients, the heterogeneity of the symptom profiles should be further explored in longitudinal studies to aid in understanding any patterns in onset of symptoms, progression and possible long-term implications.

Conclusion

The manifestation of symptoms in patients with long COVID-19 impacts all aspects of daily life, particularly neurocognitive and mental health issues. To the best of our knowledge, this is the first study to report a conceptual model of long COVID-19 with neurocognitive and emotional concepts, based on empirical evidence from patient and clinician interviews. The concepts considered important for patients could be considered for inclusion in patient-reported instruments for use in the clinical setting and future clinical trials.

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Competing interests

DR is a Regeneron Pharmaceuticals, Inc. employee/stockholder and former Roche employee, and current stockholder. SS-K, YZ, MH, TDN, and GPG are employees/stockholders at Regeneron Pharmaceuticals, Inc. JYC, and KP are employees of Modus Outcomes, and consulted for Regeneron Pharmaceuticals, Inc. AJP reported receiving personal fees from Regeneron Pharmaceuticals, Inc during the conduct of the study, personal fees from Imvaria, Boehringer Ingelheim, EBSCO/Dynamed, and Roche outside the submitted work. EM reports payments to his institution received from SciClone Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Pfizer, Chemic Labs/KODA Therapeutics, Cidara, and Leidos Biomedical Research Inc./NCI; and reports Advisory board: Basilea, and grants from NIH/NIAID, NIH/NIGMS, and BARDA.

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Author contributions

DR contributed to conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing (original draft, review, and editing). SS-K contributed to conceptualization, supervision, and writing (review and editing). JYC contributed to interview conduct, data curation, formal analysis, project administration, visualization, and writing (review and editing). KP contributed to interview conduct, data curation, formal analysis, project administration, supervision, visualization, and writing (review and editing). YZ contributed to operations, and writing (review and editing). MH contributed to conceptualization, supervision, and writing (review and editing). TDN contributed to operations, and writing (review and editing). AJP contributed to supervision, and writing (review and editing). EM contributed to supervision, and writing (review and editing). GPG contributed to conceptualization, supervision, and writing (review and editing).

Data availability statement

No additional data available.

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Table 1. Patient demographic and clinical characteristics

Variable	All (N=41)	Clinical trials (n=18)	Recruited (n=23)
Age, mean (SD)	53.56 (10.24)	56.44 (11.01)	51.30 (9.20)
Gender, n (%)			
Female	35 (85.4)	14 (77.8)	21 (91.3)
Male	6 (14.6)	4 (22.2)	2 (8.7)
Race, n (%)*			
White/Caucasian	30 (73.2)	12 (66.7)	18 (78.3)
Black/African American	9 (21.9)	4 (22.2)	5 (21.7)
American Indian/Alaskan	1 (2.4)	0 (0.0)	1 (4.3)
Asian	1 (2.4)	0 (0.0)	1 (4.3)
Other	2 (4.9)	1 (5.5)	1 (4.4)
Prefer not to answer	1 (2.4)	1 (5.5)	0 (0.0)
Self-reported health information at the time of the interview			
General health ratings, n (%)			
Excellent	3 (7.3)	2 (11.1)	1 (4.3)
Very good	3 (7.3)	3 (16.7)	0 (0.0)
Good	14 (34.1)	7 (38.9)	7 (30.4)
Fair	15 (36.6)	5 (27.8)	10 (43.5)
Poor	6 (14.6)	1 (5.5)	5 (21.7)
COVID-19 vaccination status, n (%)			
One dose of Pfizer/BioNTech	2 (4.9)	0 (0.0)	2 (8.7)
Two doses of Pfizer/BioNTech	11 (26.8)	5 (27.8)	6 (26.1)
Two doses of Moderna	11 (26.8)	8 (44.4)	3 (13.0)
One dose of Johnson & Johnson	1 (2.4)	0 (0.0)	1 (4.3)

Two doses of Pfizer/BioNTech AND a booster shot	3 (7.3)	0 (0.0)	3 (13.0)
Two doses of Moderna AND a booster shot	1 (2.4)	0 (0.0)	1 (4.3)
No COVID-19 vaccine received	12 (29.3)	5 (27.8)	7 (30.4)
Number and duration of symptoms, mean (SD)			
Time since symptoms began (months)	12.15 (5.87)	7.72 (2.11)	15.61 (5.53)
Number of symptoms reported per patient	7 (4.73)	6 (4.48)	8 (4.87)
Time between hospitalisation due to COVID-19 and interview (months)			
Not hospitalised, n (%)†	21 (51.2)	8 (44.4)	13 (56.5)
Mean (SD)	10.4 (4.95)	7.00 (6.67)	13.8 (5.05)
Self-reported comorbidities,‡ n (%)			
Hypertension/high blood pressure	18 (43.9)	5 (27.8)	13 (56.5)
Arthritis	16 (39.0)	7 (38.9)	9 (39.1)
Other§	19 (46.3)	6 (33.3)	13 (56.5)
Asthma	10 (24.4)	3 (16.7)	7 (30.4)
Diabetes (type 1, type 2, gestational)	9 (22.0)	3 (16.7)	6 (26.1)
Mood disorders (bipolar disorder, cyclothymia, etc.)	7 (17.1)	2 (11.1)	5 (21.7)
Cardiovascular disease (eg, heart failure, coronary artery)	5 (12.2)	0 (0.0)	5 (21.7)
Chronic obstructive pulmonary disease	5 (12.2)	2 (11.1)	3 (13.0)
Neurological conditions (eg, Parkinson's disease)	5 (12.2)	1 (5.5)	4 (17.4)
History of stroke	4 (9.8)	1 (5.5)	3 (13.0)
Cancer	2 (4.9)	2 (11.1)	0 (0.0)
None of the above	7 (17.1)	4 (22.2)	3 (13.0)

COVID-19, coronavirus disease 2019; SD, standard deviation.

*Patients could select more than one choice.

†Missing data included in calculation of percentages.

‡Patients could select more than one choice.

§Other refers to a comorbidity that was described only once and includes, but is not limited to, HIV/AIDS, multiple sclerosis, hypothyroidism, obesity, Hashimoto's disease, etc.

Table 2. Overview of clinicians' backgrounds

Current position(s)	Specialty/training	Number of years practicing	Number of long COVID-19 patients treated per week
Attending physician at academic medical centre	Pulmonary and critical care	30	40
Solo private practice	General medicine	20	20
Attending physician in emergency department	Emergency medicine	15	Missing
Registered nurse at a hospital	Registered nurse	30	10–20
Registered nurse at a hospital	Registered nurse	26	Missing

COVID-19, coronavirus disease 2019.

Figure 1. Literature review process for concepts related to symptoms and impact concepts

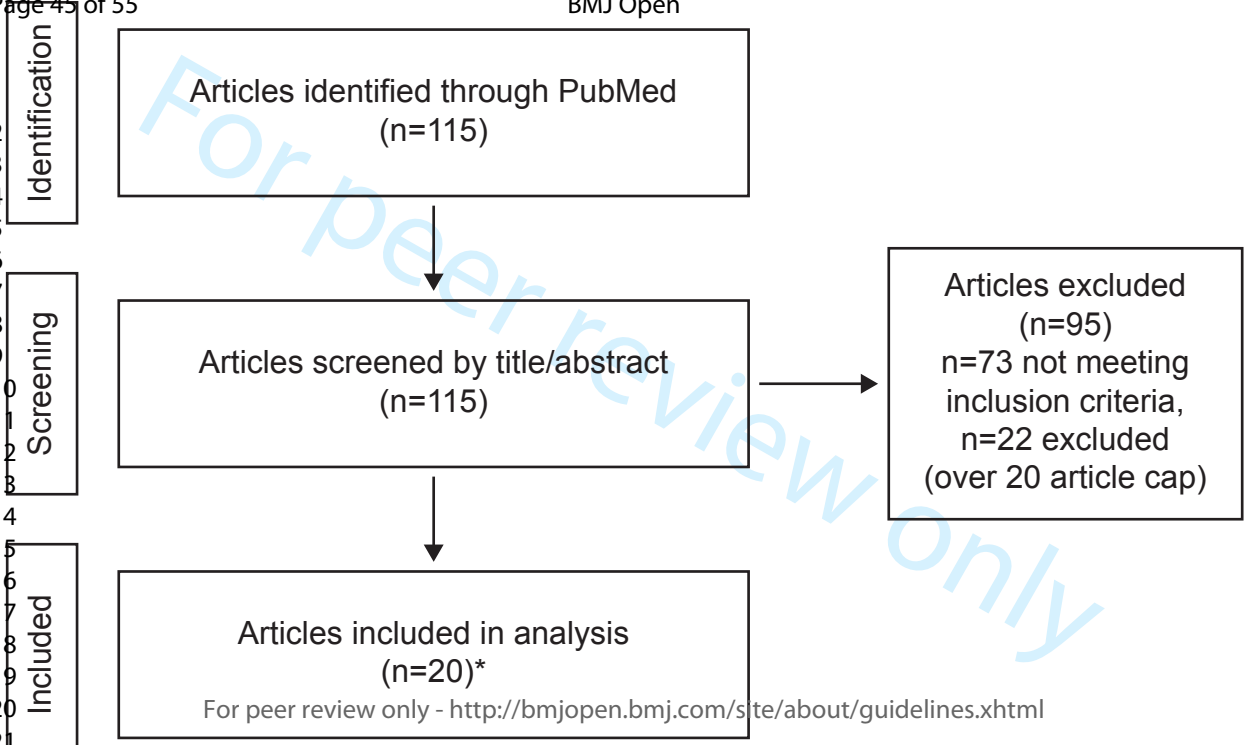
*It was decided *a priori* that the full text of up to 20 articles would be reviewed.

Figure 2. Detailed conceptual model describing the patient experience of long COVID-19

*Supported by patients' interviews.

†Supported by clinician interviews.

‡Reported in literature.



Key

Domain	Domain
Sub-domain	Sub-domain

Symptoms

Upper respiratory tract
- Phlegm*,†,‡
- Runny nose and sneezing*,‡
- Sore throat‡
- Dry mouth*,‡

Lower respiratory tract
- Shortness of breath*,†,‡
- Cough*,†,‡
- Chest pain*,†,‡
- Difficulty breathing*

Smell and taste
- Altered or loss of taste*,†,‡
- Altered or loss of smell*,†,‡

Systemic
- Fatigue*,†,‡
- Weakness*,†,‡
- Joint pain*,‡
- Muscle aches and pain*,†,‡
- Body aches and pain*,‡
- Stiffness*
- Fever*,†,‡
- Chills*,†
- Hot flashes†
- Sweats*,†,‡
- Heart palpitations*,†,‡
- Changes to menstrual cycle*

Gastrointestinal
- Nausea*,‡
- Difficulty swallowing*
- Digestive problems (abdominal pain, bloating, diarrhoea, constipation)*,‡

Neuro-cognitive
- Numbness*,†,‡
- Pins and needles*,‡
- Ringing in ears*,†,‡
- Dizziness*,†,‡
- Lightheaded*,†
- Headache*,†,‡
- Haziness†,‡
- Confusion*
- Forgetfulness/ memory problems*
- Brain fog*,†,‡
- Concentration*,†,‡
- Difficulties finding the right word*,†,‡
- Challenges with fine motor skills*

Other
- Skin changes*,†,‡
- Red or dry eyes*,†,‡
- Vision changes*,‡

Impacts

Activities of daily living
- Eating*
- Drinking*
- Getting up from a bed or chair*
- Bathing*

Instrumental activities of daily living
- Household chores*,‡
- Child care*
- Challenges caring for pets*
- Cooking*
- Shopping*
- Loss of independence*

Physical impacts
- Sleep disturbance*,†,‡
- Need to nap*
- Exercise*,†,‡
- Ability to walk/climb stairs*
- Hair loss*,†,‡
- Decrease in Appetite and weight loss*,†,‡

Emotional
- Anxiety*,†,‡
- Depression*,†,‡
- Fear of reinfection*
- Frustration*,‡
- Heightened emotional responses*
- Irritability*
- Indifference*
- Not recognising oneself*
- (Post-traumatic) stress‡

Leisure/social
- Cautious about travel*
- Isolation*,‡
- Housebound*
- Feeling like a burden on families*,‡
- Engaging in fewer social activities*

Professional
- Ability to work full-time*,‡

Supplementary material

Supplementary methods

Process of patient recruitment by Rare Patient Voice and PRC Corporation

1. Recruiters invited potentially eligible patients to participate via email or telephone, using institutional review board-approved language.

2. Those interested in participating communicated with a trained recruiter via phone or email and confirmed whether they met the inclusion/exclusion criteria.

3. Patients were asked to provide verbal consent for their contact details to be provided to a Modus researcher and to participate in the study. Written informed consent was obtained electronically prior to patients' participation in the study. All patients were provided a copy of the fully signed consent form.

4. Patients were also asked to provide written confirmation from their clinician of their long coronavirus disease 2019 (COVID-19) diagnosis.

Screener form eligibility criteria

Inclusion criteria

- ≥18 years of age

- Clinically confirmed diagnosis of long COVID-19

- Initial COVID-19 infection must have been at least 180 days ago (documented via a positive polymerase chain reaction test)

- Currently experiencing long COVID-19 symptom(s) that cannot be explained by an alternative diagnosis
- The patient was not vaccinated at the time of the COVID-19 infection or 90 days thereafter
- The patient has received their last COVID-19 vaccination (including booster shot) at least 4 weeks prior to scheduling the interview
- Willingness and ability to participate in up to one 60-minute audio-recorded telephone or online interview in English
- Willingness and cognitive ability to provide electronic, informed consent
- Ability to speak, read, write and understand English
- Patient has any of the following risk factors for severe COVID-19:
  - Age ≥50 years
  - Obesity, defined as body mass index (BMI) ≥30 kg/m^2, or BMI (kg/m^2) ≥95th percentile for age and sex based on Centers for Disease Control and Prevention growth charts
  - Cardiovascular disease, including hypertension
  - Chronic lung disease, including asthma
  - Type 1 or type 2 diabetes mellitus
  - Chronic kidney disease, including those on dialysis

  - Immunosuppressed (cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, or prolonged use of immune-weakening medications

Exclusion criteria

- Patient has concomitant illness(es) that in the recruiter or investigator's judgment would confound researchers' understanding and description of the long COVID-19 disease experience
- Patient was hospitalised during initial COVID-19 infection

Table S1. PubMed search strategy

Search	Term(s)	Results
1	Post-acute sequelae of SARS-CoV-2 infection OR long COVID-19 *Field: Title/Abstract*	134
2	Symptoms	7,204,054
3	Impact	1,262,676
4	Qualitative	325,386
5	Functioning	14,448,823
6	Health-related quality of life	445,770
7	1 AND 2 OR 3 OR 4 OR 5 OR 6	171
8	Filters: English, human participants	115

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S2. Saturation analysis of sub-domains: Symptoms

Group 1 (interviews 1–8) 24 concepts	Group 2 (interviews 9–16) 7 concepts	Group 3 (interviews 17–24) 7 concepts	Group 4 (interviews 25–32) 1 concept	Group 5 (interviews 33–41) 2 concepts
Altered or loss of smell	Chest pain	Digestive problems (abdominal pain, bloating, diarrhoea, constipation)	Difficulty swallowing	Challenges with fine motor skills
Altered or loss of taste	Dizziness	Skin changes		Stiffness
Body aches and pains	Dry mouth	Joint pain		
Brain fog	Fever	Lightheaded		
Chills	Vision changes	Decrease in appetite and weight loss		
Cough	Pins and needles	Muscle pain		
Difficulty breathing	Numbness	Changes in menstrual cycle		
Concentration	Fever			
Difficulties finding the right word				
Fatigue				
Hair loss				
Headache				
Heart palpitations				
Haziness				
Forgetfulness/ memory problems				
Nausea				
Phlegm				

Red or dry eyes
Ringing in ears
Runny nose
Shortness of breath
Sneezing
Sweats
Weakness

Table S3. Saturation analysis of sub-domains: Impacts

Group 1 (interviews 1–8) 10 concepts	Group 2 (interviews 9–16) 11 concepts	Group 3 (interviews 17–24) 1 concept	Group 4 (interviews 25–32) 0 concepts	Group 5 (interviews 33–41) 0 concepts
Anxiety	Sleep disturbance	Challenges caring for pets		
Depression	Bathing			
Childcare	Independently moving around			
Irritability	Feeling like a burden on families			
Cautious about travel	Housebound			
Cooking	Drinking			
Exercise	Eating			
Household chores	Fear of reinfection			
Isolation	Stress			
Engaging in fewer social activities	Shopping			
	Loss of independence			

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	3–4
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	6–7
Purpose or research question - Purpose of the study and specific objectives or questions	7–8
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	9–10
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	9–10, Table 2
Context - Setting/site and salient contextual factors; rationale**	9–12, Tables S1
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	11
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	12
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	9–10

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	9–10
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	15, Tables 1 & 2
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	11–14
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	12–14, Tables S2 & S3
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	12–14

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	15–22
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	18–22

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	23–26
Limitations - Trustworthiness and limitations of findings	25, 5

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	28
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	28

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
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BMJ Open

Thematic analysis to explore patients' experiences with long COVID-19: a conceptual model of symptoms and impacts on daily lives

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Thematic analysis to explore patients' experiences with long COVID-19: a conceptual model of symptoms and impacts on daily lives

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Abstract

Objectives: There is limited qualitative research on patients' experiences with long coronavirus disease 2019 (COVID-19), and how specific symptoms impact their daily lives. The study aimed to understand patients' lived experience of long COVID-19, and to develop a conceptual model representing the symptoms and their impact on overall quality of life.

Setting: Qualitative study consisting of a comprehensive literature review, and in-depth clinician and patient semi-structured interviews.

Participants: Forty-one adult patients with long COVID-19, of whom 18 (44%) were recruited through Regeneron Pharmaceuticals Inc.'s clinical trials and 23 (56%) through recruitment agencies; 85.4% were female and 73.2% were White. Five independent clinicians treating patients with long COVID-19 were interviewed. Concept saturation was also assessed.

Primary and secondary outcomes: Interview transcripts were analysed thematically to identify concepts of interest spontaneously mentioned by patients, including symptoms and their impacts on daily life, to guide development of the conceptual model.

Results: Findings from the literature review and clinician and patient interviews resulted in the development of a conceptual model comprising two overarching domains: symptoms (upper respiratory tract, lower respiratory tract, smell and taste, systemic, gastrointestinal, neuro-cognitive and other) and impacts (activities of daily living, instrumental activities of daily living, physical impacts, emotional, social/leisure activities

and professional impacts). Saturation was achieved for the reported impacts. The symptoms reported were heterogenic; neuro-cognitive symptoms, such as numbness, ringing in ears, haziness, confusion, forgetfulness/memory problems, brain fog, concentration, difficulties finding the right word, and challenges with fine motor skills, were particularly pertinent for several months.

Conclusion: The conceptual model, developed based on patient experience data of long COVID-19, highlighted numerous symptoms that impact patients' physical and mental wellbeing, and suggest humanistic unmet needs. Prospective real-world studies are warranted to understand the pattern of long COVID-19 experienced in larger samples over longer periods of time.

Word count: 297/300 words

Strengths and limitations of this study (up to five bullet points)

- This study included a comprehensive review of published literature related to long coronavirus disease 2019 (COVID-19), alongside in-depth, qualitative interviews with patients recruited from both clinical trials and healthcare research firms, as well as interviews with independent clinicians, to understand the patient experience of long COVID-19.
- While knowledge about acute COVID-19 symptoms and patient experience is relatively comprehensive, this study adds to the limited literature on the patient experience of long COVID-19 and its impacts on daily life, including neurocognitive, physical and emotional functioning.
- A limitation of this study is that the participants were predominantly White and female. Whilst the pathology of long COVID-19 is known to affect mostly women, it would be desirable to perform additional research in males and more diverse patient groups for better representation of the affected population.

Introduction

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), can experience long-term effects even if the virus is no longer detected with standard methods [1]. These effects are often referred to as "long COVID", "post-COVID-19 syndrome" or "post-acute sequelae of SARS-CoV-2" [2-4], and definitions may vary. According to the Centers for Disease Control and Prevention (CDC), patients with long COVID-19 continue to experience symptoms for ≥4 weeks after the initial infection with SARS-CoV-2 [1]. The National Institute for Health and Care Excellence (NICE) uses the term "post-COVID-19 syndrome" and defines it as "*signs and symptoms that develop during or after an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis"* [5]. While the World Health Organization (WHO) defines the condition as *"the illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within 3 months from the onset of COVID-19, with symptoms and effects that last for at least 2 months."* Similar to the NICE guidelines, the WHO specifies that *"the symptoms and effects of post COVID-19 condition cannot be explained by an alternative diagnosis"* [6].

The most commonly reported symptoms of long COVID-19 in current literature are fatigue, chest pain, muscle aches, persistent cough, fever, shortness of breath or difficulty breathing, loss of smell or taste, depression or anxiety, trouble speaking, memory, concentration and/or sleep problems [1, 6-10]. The CDC and NICE have indicated that long COVID-19 can affect anyone who has been infected, regardless of the severity of the initial infection [1, 5]. However, risk factors for long COVID-19 have

been reported to include female sex, older age and a history of more than five symptoms during the infection [11, 12]. Specific features of long COVID-19 have been identified via immune profiling, and include elevated humoral responses against SARS-CoV-2, and decreased levels of cortisol [13]. The reported prevalence of long COVID-19 ranges considerably, from 8% to 57% depending on the source and patient population evaluated [1, 14, 15]. A recent study reported an elevated risk of both hospitalisation and death during two years of follow up for patients who were hospitalised during acute COVID-19 infection [16]. While the exact prevalence of long COVID-19 is unclear, it is evident that management of patients with the disease poses a potentially significant burden for healthcare systems globally [17]. The health and economic consequences of long COVID-19 are predicted to be in line with acute disease; when calculating for a reduced quality-adjusted life expectancy, long COVID-19 has been estimated to cost around $2.6 trillion in the USA [18, 19].

Although COVID-19 is a global public health issue, and there is an increasing body of clinical and epidemiological literature on the incidence and prevalence of symptoms, to date there has been little empirical evidence directly from patients regarding the symptoms associated with long COVID-19 and how these symptoms impact their lives [7, 20-23]. Previously, we reported that the manifestation of symptoms in patients who were diagnosed with COVID-19 was heterogeneous and significantly affected all aspects of patients' lives; however, the study focused on patients with acute disease [24]. Due to its discrete characteristics, it is essential to understand and study long COVID-19 separately from acute COVID-19. We therefore sought to: (i) gain an in-depth understanding of the patient experience of long COVID-19 symptoms and the

impact on their daily lives; and (ii) understand the patient experience within the framework of a conceptual model based on empirical patient-relevant evidence informed by literature and patient and clinician interviews.

Methods

Literature review

Search strategy

An electronic search was performed on July 23, 2021, using PubMed to identify qualitative papers published up to that date that explored the patient experience of long COVID-19. A combination of search terms related to the target population were used, including (**Table S1**): post-acute sequelae of SARS-CoV-2 infection, long COVID-19, and patient experience (eg, symptoms, impacts). The search was limited to humans and English language publications. During the first stage of screening, articles were reviewed by title and abstract only. The second screening stage included full-text review of articles that were retained after the first screening. It was decided a priori that the full text of up to 20 articles would be reviewed.

Qualitative in-depth interviews with patients and clinicians

Patients

A purposive sample of patients was initially identified through Regeneron Pharmaceuticals Inc.'s clinical trial programme (COV-2066 in hospitalised participants [NCT04426695] and COV-2067 in non-hospitalised participants [NCT04425629]) [25, 26]. This patient sample was extended to the real-world through two independent healthcare research firms, Rare Patient Voice and PRC Corporation, which specialise in the recruitment of difficult-to-reach populations (**Supplementary Methods)**. Adults (aged ≥18 years) with a positive SARS-CoV-2 polymerase chain reaction test ≥180

days prior to enrolment into this study, experiencing long COVID-19 symptom(s) that could not be explained by an alternative diagnosis, and who were willing and able to participate in one 60-minute audio-recorded telephone or online interview in English, were included in the study. Full inclusion and exclusion criteria are provided in the **Supplementary Methods**, along with details of patient information collected.

Clinicians

Clinicians were eligible to participate if they were regularly seeing/treating more than five patients a week with long COVID-19 in the USA, and were willing to participate in a 60-minute audio-recorded telephone interview in English. Clinicians who only treated patients who resided in an institutional setting (eg, nursing home) were excluded. There were no pre-defined sample quotas set for the five clinicians; however, the recruitment process sought a diverse representation of professions (eg, general practitioners, nurses), specialties, and treatment settings (eg, hospital/non-hospital settings) where patients with long COVID-19 were regularly treated. A heterogeneous sample of five clinicians, who served as research consultants, was considered sufficient to obtain insights for input into the conceptual model.

Sampling

A purposive sampling approach was used and initially defined to target patients who were enrolled in Regeneron Pharmaceuticals Inc.'s clinical trials in the long COVID-19 sub-study in the USA. Additional recruitment of patients from external recruitment agencies were matched to the trial patients according to inclusion criteria. Due to the

heterogeneity of both long COVID-19 symptoms and the affected population [27], sampling covered a target population experiencing a range of symptoms. This ensured a diverse sample of up to 50 patients, which was estimated as an adequate sample size to reach conceptual saturation in the concepts of interest (COIs) [28, 29]. The sample size was anticipated to be adjusted downward based on recruitment feasibility and saturation analysis. In qualitative research, whether the sample size to obtain probable symptoms and impacts from a population is substantial or not is usually defined by the principle of data saturation (see below) [30]. The final sample size was to be determined by saturation based on good research practice [28, 31] and requirements by the US Food and Drug Administration (FDA) for establishing content validity [32].

Patient and clinician interviews

Semi-structured patient interview guides were developed in line with best practices outlined in the FDA patient-focussed drug development guidance [33]. The patient interview guides provided the researcher with a general outline for the semi-structured interview, but each interview was unique based on spontaneous patient responses to questions about symptoms and the impacts of long COVID-19 on daily activities and health-related quality of life. Audio-recorded patient interviews were conducted via Microsoft Teams (use of camera optional by patient) by four experienced qualitative researchers who received specific training for this study, and who had backgrounds in psychology and anthropology as well as ≥2 years' experience in qualitative research. During the semi-structured interview, patients were asked open-ended questions to provide spontaneous inputs regarding the symptoms of long COVID-19 (experienced after the first 4 weeks of acute COVID-19). For example, 'Can you begin by telling me

about the symptoms you have experienced with long COVID-19? and 'How would you describe these symptoms in your own words?' and the impacts the symptoms had on the patients' daily lives. For example, 'In what ways has your day-to-day life changed since you began to experience long COVID-19 symptoms?' Specific questions for each reported symptoms were also asked, which included the symptom duration, as well as any changes over time such as improvement or worsening, and symptom severity over time. Additional questions asked for further descriptions of symptoms and which symptoms were the most and least bothersome. Emotional impacts, effects on social interactions and disruption to day-to-day life and activities were also explored. Examples of these questions are, 'How do your long COVID-19 symptoms affect your day-to-day life? And 'Are there day-to-day activities that you engage in differently since experiencing long COVID-19 symptoms?'. Additional questions on activities were to assess the patients' emotional wellbeing (e.g. anxiety or depression) and their ability to engage in physical activities and their usual exercise routine, to care for other people and pets, to spend time with others, to do their usual hobbies and to do grocery shopping.

Clinician interviews were also conducted by experienced qualitative researchers via Microsoft Teams. During the interview process, clinicians provided insights into patients' experiences of long COVID-19. All relevant findings extracted from the articles in the literature review and the clinician interviews were organised into a conceptual model to detail all potential COIs that could inform the patient experience of long COVID-19.

Ethical approval

All study documents (the protocol, interview guides, demographic and health information form, screener form and informed consent form) were approved by the Western Institutional Review Board-Copernicus Group Independent Review Board (IRB) before study initiation (IRB tracking # 20214272). Electronic informed consent was obtained from all patients. Patients were paid a fee in line with fair market value to cover the time taken to participate in the study.

Thematic data analysis

All interviews were audio recorded and transcribed verbatim. Transcripts from patient interviews were analysed thematically [34], using detailed line-by-line open and inductive coding [35-37] within ATLAS.ti software (Scientific Software Development GmbH). Coding was tailored to the research objectives of the study, which were the identification of symptoms and impacts of long COVID-19, including those spontaneously mentioned by patients as well as further probing of COIs. Codes and quotations were compared with the rest of the data and inductively categorised into higher-order overarching categories referred to as concepts, sub-domains and domains, reflecting their conceptual content underpinning. This categorisation was an iterative process performed by a research team that involved comparison and cross-referencing between different analytic categories.

Saturation analysis

Details of the saturation analysis are provided in the **Supplementary Methods**.

Conceptual model

A conceptual model identifies and characterises COIs related to a health condition [38]. To develop a conceptual model of patient experiences with long COVID-19, data extracted from the literature review were inductively categorised into higher-order conceptual domains. Once coding was complete, a preliminary conceptual model was developed using the concepts extracted from PubMed; this was then revised with clinician input and further refined based on the results from patient interviews. Each concept was then considered and grouped into higher-order domains. If a concept was repeated across multiple sources, it was listed once. Ultimately, standard analytical techniques of conceptual model development were used to develop a visual representation of how the COIs relate to each other, grounded in a data-driven process based on patient-relevant empirical evidence [35-37, 39].

Analysis

Analysis details are provided in the **Supplementary Methods**.

Results

Literature review findings

The PubMed search of qualitative studies identified 115 abstracts for screening: 95 articles were excluded after abstract review and 20 full-text articles related to symptom and impact concepts were included in the final literature analysis (**Figure 1**). Articles presented symptoms at different conceptual levels (domain, sub-domains and concepts). Impacts were also presented at a high level of abstraction, eg, worsened quality of life.

Patient demographics and interviews

Interviews were conducted between 30 September 2021, and 12 May 2022. The study included 41 patients, of whom 18 (44%) were recruited through clinical trials and 23 (56%) through recruitment agencies (**Table 1**). The mean age was 53.6 years, 85% were female and 73% were White. The mean time between the start of any COVID-19 symptoms and the interview was 12 months (range: 1–25 months). Twenty-two patients (54%) received two doses of either the Moderna (27%) or the Pfizer/BioNTech (27%) vaccine, and 49% had been hospitalised. Most patients reported good (34%) or fair (37%) general health. At the time of the interview, hypertension/high blood pressure, arthritis, asthma, diabetes and mood disorders were self-reported by 18 (44%), 16 (39%), 10 (24%), nine (22%) and seven (17%) patients, respectively.

Clinician interviews

Participating clinicians included nurses and physicians who treated between 10 and 40 patients a week for COVID-19 (**Table S2**). All clinicians considered the CDC [1],

WHO [6] and NICE [5] guidelines (of ≥4 weeks after initially experiencing COVID-19 symptoms that cannot be explained by another condition) as the most appropriate timepoint for describing symptoms of long COVID-19, reasoning that they expected symptoms like cough to typically resolve after the acute phase of COVID-19 within this time frame.

Clinicians described fatigue, shortness of breath, chest pain/discomfort, cough, and loss of smell and taste as the most common symptoms experienced by patients with long COVID-19. In addition, they emphasised that long COVID-19 may affect any system of the body and that there was a wide variety of other, less common symptoms, such as headache, dizziness and hair loss. One clinician highlighted that many patients received a combination of treatments in relation to their symptoms, and that it became challenging to distinguish between less common symptoms related to long COVID-19 and the side effects of these treatments.

Clinicians reported that cognitive impairment accompanied common and less common symptoms, highlighting several mental health components such as depression, anxiety and feeling vulnerable. Additional impacts on quality of life included loss of appetite, sleep interruptions, lack of physical activity, inability to work and inability to perform activities of daily living (ADLs). Clinicians noted that most patients presented with ongoing symptoms from their initial COVID-19 diagnosis; of these, some presented cyclically. They also reported that a small number of patients who presented with severe respiratory symptoms were hospitalised, but most received care in outpatient settings. During the interviews, clinicians suggested that most symptoms would eventually resolve, though they found it challenging to say exactly when this would happen.

Conceptual model development and saturation

Data from the literature review and clinician/patient interviews yielded two overarching domains: symptoms and impacts. The refined conceptual model is presented in **Figure 2**. Information was added in the conceptual model about the source of concepts included (literature review, clinician interviews and/or patient interviews). All patient-reported concepts included in the model were reported by at least two patients.

Of the 41 symptoms presented, 93% were identified in the first 24 interviews (**Table S3**). In the remaining group of nine interviews, only two additional sub-domains were identified: challenges with fine motor skills, and stiffness. Stiffness added granularity to the body aches/pain sub-domain previously identified and, with the highly heterogeneous nature of long COVID-19, we can expect that additional symptoms would emerge with additional interviews. This indicated that the current analysis was comprehensive regarding the key symptom domains. For sub-domains in the impact domain, all unique sub-domains (n=22) were identified in the first three groups of the saturation analysis (**Table S4**). No new impacts emerged in the final 16 interviews. This indicated that saturation was achieved for the reported impacts.

Symptoms

Symptoms experienced after the first 4 weeks of acute COVID-19, as reported by patients, were elicited during patient interviews. Symptoms were grouped into seven domains: upper respiratory tract, lower respiratory tract, smell and taste, systemic, gastrointestinal, neurocognitive, and other. Due to the variation and complexity of symptoms experienced, the domains extended across specific areas of the body (ie,

upper respiratory tract) to more general subdomains (ie, weakness or aches in the systemic domain, not exclusive or specific to one area of the body). A selection of quotations covering these symptoms is presented in **Table 2** to reflect the broad and often debilitating nature of symptoms of long COVID-19 experienced by patients.

The upper respiratory tract domain reflected issues related to the sinuses and throat, and included symptoms such as phlegm, runny nose and sneezing, difficulty swallowing, and dry mouth. Difficulty in swallowing was described by one patient as like choking. The lower respiratory tract domain reflected issues related to the airways and lungs, and the sub-domains reflected symptoms such as shortness of breath, cough (including dry cough), difficulty breathing and chest pain. Loss of smell and taste was a commonly reported symptom in patients with long COVID-19. The severity of loss of senses varied widely, with some patients describing a total loss, while others reported that their senses were altered. The systemic domain included various symptoms which affected the entire body, rather than a single organ or body part, such as fatigue, weakness, heart palpitations, body aches, joint pain, fever, stiffness and chills. Fatigue was specifically described by patients in terms of its severity, whether it improved or not, and how variable the fatigue was. The gastrointestinal symptoms reported were nausea, diarrhoea vomiting, and other stomach-related issues. Many patients experienced neurocognitive symptoms such as brain fog, dizziness, memory problems, difficulties finding the right word, and challenges with fine motor skills. Brain fog reflected the challenges patients experienced to focus and stay on task. Neurocognitive symptoms were particularly pertinent for extended periods of times, with some patients reporting symptoms for several months.

Impact on daily life

The overarching domain “impacts” is defined by the activities and health-related quality of life experiences that patients report have been affected because of having long COVID-19. “Impacts” covered six sub-domains related to ADLs, instrumental activities of daily living (IADLs), physical impacts, emotional, social/leisure activities and professional impacts. A selection of quotations covering these domains is presented in **Table 3** to reflect the diverse and inconvenient negative impacts of long COVID-19 experienced by patients.

Quotations were categorized into ADLs if they referred to activities related to eating, drinking, getting up from a bed or chair, climbing stairs, and routines of self-care (eg, bathing). IADLs included activities related to household chores, taking care of children or pets, shopping and meal preparation. The physical impacts domain included sub-domains related to concepts associated with physical changes, such as changes to appetite and weight loss, hair loss and sleep disruption. It also included impacts on the ability to perform physical tasks such as walking and exercising. The emotional domain included sub-domains associated with changes in the patient’s psyche and mood in general, including issues associated with various worries and anxieties of having long COVID-19, depression, irritability, frustration, heightened emotional responses and not recognising oneself any longer. Activities related to social life, hobbies and leisure activities as well as sports and exercise were categorised under social and leisure activities. The professional domain captured changes in the patient’s ability to work.

Discussion

There is limited information on the patient experience of living with long COVID-19, and to our knowledge there is no current conceptual model that provides a visual representation of the symptoms and impacts of the disease. This qualitative study provides novel insight into the conceptualisation of the patient experience of long COVID-19. These rich patient qualitative insights are a useful resource to guide support and treatment requirements of those with long COVID-19 [40].

Following in-depth patient and physician interviews, we summarised the data captured in a simple and clinically grounded conceptual model comprising upper and lower respiratory symptoms, systemic symptoms, gastrointestinal symptoms, neuro-cognitive symptoms, altered or loss of smell and taste, and other symptoms. These symptoms were consistent with those reported by national and international health bodies such as the CDC [1], WHO [6] and NICE [5], and by systematic reviews [27, 41]. In addition to headache, dizziness and lightheadedness, which were also identified in the acute COVID-19 conceptual model [24], the long COVID-19 conceptual model included various neurocognitive symptoms such as numbness, ringing in ears, haziness, confusion, forgetfulness/memory problems, brain fog, concentration, difficulties finding the right word, and challenges with fine motor skills, and some of these symptoms were reported to be experienced for several months. Furthermore, while emotional concepts such as anxiety, depression, irritability and frustration were presented in the acute COVID-19 conceptual model [24], in the patients with long COVID-19 additional concepts included fear of reinfection, heightened emotional responses, indifference, not recognising oneself, and post-traumatic stress. At the time

our study was initiated, no other instruments were available to assess the impact of long COVID-19. Subsequently several instruments are now available. The modified COVID-19 Yorkshire Rehabilitation Scale, Symptom Burden Questionnaire for Long Covid, and post-acute (long) COVID-19 quality of life instrument each assess symptom burden in long COVID-19, but are not comprehensive in all symptoms identified in our model; particularly neurocognitive symptoms [42-44]. However, a handful of qualitative studies have demonstrated that patients with long COVID-19 report a very low state of mind and felt that their self-identity was affected, findings that are consistent with our own [21, 45]. Neuro-rehabilitation programmes for patients with long COVID-19 have proved helpful to improve working memory, verbal fluency and anxious-depressive symptomatology [46]. Our study further highlights the importance of understanding the impact these neurocognitive symptoms, which are not often reported during acute disease, can have on patients' emotional, social and professional lives.

In addition to symptoms, we also captured the impact of long COVID-19 and the changes in the daily lives of affected patients. The range of impacts due to long COVID-19 was consistent with those experienced during acute disease [24]; however, this study highlighted the emphasis on long-term impacts. A reduction in the number and/or severity of symptoms may mitigate the negative impact of long COVID-19 on patient health-related quality of life. Studies in populations with acute COVID-19 have shown that improvements in symptoms are correlated with improvements in outcomes and patient quality of life. However, additional qualitative and quantitative research is required to address this current knowledge gap, and further explore how management of symptoms in long COVID-19 could improve patients' lives.

Our study has two main limitations. First, the patients who were recruited from the external healthcare research firms closely matched the inclusion and exclusion criteria from the clinical trials. This approach may have resulted in a missed profile of patients with long COVID-19 who may be experiencing symptoms differently. Additional interviews with a broader exclusion and inclusion criteria could be considered as future research to determine whether they experience symptoms differently. Second, most of the patients in the present study were female and White. Nevertheless, this is consistent with other studies where the persistence of long COVID-19 symptoms for ≥12 weeks was higher in females than males [47]. There have also been reports on differences in prevalence of long COVID-19 symptoms in different ethnicities. One study that utilised data from community-based samples (>600,000) reported that an Asian population had a lower risk of persistent symptoms compared to a White population [47]. However, in other studies, Black Afro-Caribbean ethnic groups and other minority ethnic groups (native American, Middle Eastern or Polynesian) had a higher risk of long COVID-19 compared to a White population [12]. Additional studies are needed in different ethnic groups to fully understand the presentation and impact of long COVID-19 in different populations.

The present qualitative study provides unique and valuable insights on symptoms in patients with confirmed diagnoses of long COVID-19 and how it impacts their daily lives, including physical, emotional and psychological functioning. We found that patients typically experienced symptoms across of number of clinical domains during long COVID-19. Improving our understanding of the patient experience of the disease will help healthcare providers make informed decisions on optimised treatment options and

the support needed for patients to improve their overall health-related quality of life, while also easing the burden on patient's families and society [45]. Although no obvious symptomatic profiles were found during the interviews with patients, the heterogeneity of the symptom profiles should be further explored in longitudinal studies to aid in understanding any patterns in onset of symptoms, progression and possible long-term implications.

Conclusion

Our qualitative research reveals that long COVID-19 impacts all aspects of patients' daily life, particularly neurocognitive and mental health issues. To the best of our knowledge, this is the first study to report a conceptual model of long COVID-19 with neurocognitive and emotional concepts, based on empirical evidence from patient and clinician interviews. The model highlights, from a patient perspective, symptoms and impacts associated with long COVID-19, all of which showed significant negative effects on patient health-related quality of life.

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Competing interests

DR is a Regeneron Pharmaceuticals, Inc. employee/stockholder and former Roche employee, and current stockholder. SS-K, YZ, MH, TDN, and GPG are employees/stockholders at Regeneron Pharmaceuticals, Inc. JYC, and KP are employees of Modus Outcomes, and consulted for Regeneron Pharmaceuticals, Inc. AJP reported receiving personal fees from Regeneron Pharmaceuticals, Inc during the conduct of the study, personal fees from Imvaria, Boehringer Ingelheim, EBSCO/Dynamed, and Roche outside the submitted work. EM reports payments to his institution received from SciClone Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Pfizer, Chemic Labs/KODA Therapeutics, Cidara, and Leidos Biomedical Research Inc./NCI; and reports Advisory board: Basilea, and grants from NIH/NIAID, NIH/NIGMS, and BARDA.

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Author contributions

DR contributed to conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing (original draft, review, and editing). SS-K contributed to conceptualization, supervision, and writing (review and editing). JYC contributed to interview conduct, data curation, formal analysis, project administration, visualization, and writing (review and editing). KP contributed to interview conduct, data curation, formal analysis, project administration, supervision, visualization, and writing (review and editing). YZ contributed to operations, and writing (review and editing). MH contributed to conceptualization, supervision, and writing (review and editing). TDN contributed to operations, and writing (review and editing). AJP contributed to supervision, and writing (review and editing). EM contributed to supervision, and writing (review and editing). GPG contributed to conceptualization, supervision, and writing (review and editing).

Data availability statement

No additional data available.

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Table 1. Patient demographic and clinical characteristics

Variable	All (N=41)	Clinical trials (n=18)	Recruited (n=23)
Age, mean (SD)	53.56 (10.24)	56.44 (11.01)	51.30 (9.20)
Gender, n (%)			
Female	35 (85.4)	14 (77.8)	21 (91.3)
Male	6 (14.6)	4 (22.2)	2 (8.7)
Race, n (%)*			
White/Caucasian	30 (73.2)	12 (66.7)	18 (78.3)
Black/African American	9 (21.9)	4 (22.2)	5 (21.7)
American Indian/Alaskan	1 (2.4)	0 (0.0)	1 (4.3)
Asian	1 (2.4)	0 (0.0)	1 (4.3)
Other	2 (4.9)	1 (5.5)	1 (4.4)
Prefer not to answer	1 (2.4)	1 (5.5)	0 (0.0)
Self-reported health information at the time of the interview			
General health ratings, n (%)			
Excellent	3 (7.3)	2 (11.1)	1 (4.3)
Very good	3 (7.3)	3 (16.7)	0 (0.0)
Good	14 (34.1)	7 (38.9)	7 (30.4)
Fair	15 (36.6)	5 (27.8)	10 (43.5)
Poor	6 (14.6)	1 (5.5)	5 (21.7)
COVID-19 vaccination status, n (%)			
One dose of Pfizer/BioNTech	2 (4.9)	0 (0.0)	2 (8.7)
Two doses of Pfizer/BioNTech	11 (26.8)	5 (27.8)	6 (26.1)
Two doses of Moderna	11 (26.8)	8 (44.4)	3 (13.0)
One dose of Johnson & Johnson	1 (2.4)	0 (0.0)	1 (4.3)

Two doses of Pfizer/BioNTech AND a booster shot	3 (7.3)	0 (0.0)	3 (13.0)
Two doses of Moderna AND a booster shot	1 (2.4)	0 (0.0)	1 (4.3)
No COVID-19 vaccine received	12 (29.3)	5 (27.8)	7 (30.4)
Number and duration of symptoms, mean (SD)			
Time since symptoms began (months)	12.15 (5.87)	7.72 (2.11)	15.61 (5.53)
Number of symptoms reported per patient	7 (4.73)	6 (4.48)	8 (4.87)
Time between hospitalisation due to COVID-19 and interview (months)			
Not hospitalised, n (%)†	21 (51.2)	8 (44.4)	13 (56.5)
Mean (SD)	10.4 (4.95)	7.00 (6.67)	13.8 (5.05)
Self-reported comorbidities,‡ n (%)			
Hypertension/high blood pressure	18 (43.9)	5 (27.8)	13 (56.5)
Arthritis	16 (39.0)	7 (38.9)	9 (39.1)
Other§	19 (46.3)	6 (33.3)	13 (56.5)
Asthma	10 (24.4)	3 (16.7)	7 (30.4)
Diabetes (type 1, type 2, gestational)	9 (22.0)	3 (16.7)	6 (26.1)
Mood disorders (bipolar disorder, cyclothymia, etc.)	7 (17.1)	2 (11.1)	5 (21.7)
Cardiovascular disease (eg, heart failure, coronary artery)	5 (12.2)	0 (0.0)	5 (21.7)
Chronic obstructive pulmonary disease	5 (12.2)	2 (11.1)	3 (13.0)
Neurological conditions (eg, Parkinson's disease)	5 (12.2)	1 (5.5)	4 (17.4)
History of stroke	4 (9.8)	1 (5.5)	3 (13.0)
Cancer	2 (4.9)	2 (11.1)	0 (0.0)
None of the above	7 (17.1)	4 (22.2)	3 (13.0)

COVID-19, coronavirus disease 2019; SD, standard deviation.

*Patients could select more than one choice to reflect individuals with mixed race.

†Missing data included in calculation of percentages.

‡Patients could select more than one choice.

§Other refers to a comorbidity that was described only once and includes, but is not limited to, HIV/AIDS, multiple sclerosis, hypothyroidism, obesity, Hashimoto's disease, etc.

Table 2. Quotations from patients on the symptoms of long-COVID-19

Concept/Domain	Respondent demographics	Quotation
Symptom: upper respiratory tract	Female, 50–59	*"I would choke on it like a bread, cracker, peanut butter, anything – pudding even, pudding would get stuck. Anything that's thick it didn't go down easy. If it was liquidy [stet] I got it to go down. Oatmeal would get stuck. Just like it was stuck there, and I'd be choking on it."*
Symptom: Lower respiratory tract	Female, 40–49	*"So the coughing was... it felt the same as COVID. It was a dry cough. I couldn't stop. It'd be like cough and I'd try to talk and here I'd start coughing again."*
Symptom: Loss of smell and taste	Female, 40–49	*"Now the coffee to me is very sour and I have to use 4–5 sugars for that sourness in my taste buds to go away. I never had a sweet tooth but the coffee itself it tastes burnt to me, I can't have it black like I used to."*
Symptom: Systemic	Female, 50–59	*"Like, I literally could sleep all day and just lay there preferably sleeping. It just feels like I weigh 1000 pounds. I have no care for the things that need to get done. I don't care to eat; I don't care to work. I don't care... It's just a malaise, tiredness, and heaviness."*
Symptom: Gastrointestinal	Female, 30–39	*"I am having issues with digestion, appetite loss, I will have food that doesn't get digested well and just goes right through. Or I will have... issues with constipation so that's varying."*
Symptom: Neurocognitive	Female, 50–59	*"A fog comes over you and you can't think what you're trying to say. It's just hard to explain. It's a very weird feeling. You're sitting there speaking and all of a sudden you can't comprehend or concentrate to find the right words when you're trying to speak."*
	Female, 50–59	*"Very much so, I am dizzy a lot. Just going up and down the stairs. I live on the second floor. I have to hang onto the railing to make sure I am not going to fall. I have to concentrate on walking down the stairs. I have to concentrate on anything that I do that requires movement from me."*
	Female, 30–39	*"I've had a few severe situations with my memory. For instance, when I first started experiencing it, it's horrible that you're used to going and just driving, simple driving and knowing your way. For me being close to home and still forgetting how to get home,*

		not retaining that, because I am kind of new to the area but still it shouldn't have been an issue."
	Male, 50–59	*"Your recall is not as quick. Me trying to remember something I should remember… It comes back but it just isn't as quick, you have to wait a little while. It's not that you can't remember it's just that recall is slower."*
	Female, 50–59	*"Grabbing things and making sure I have a hold of them properly, otherwise I might not really be holding it… So I'll be smoking a cigarette and I'll go to take a puff of the cigarette and be like where did the cigarette go and it's fallen out of my hand and I didn't even know it."*

COVID-19, coronavirus disease 2019.

Table 3. Quotations from patients on the impacts of long-COVID-19

Concept/Domain	Respondent demographics	Quotation
Impact: ADLs	Female, 50–59	*"With the lack of energy, the fatigue, the shortness of breath when I am active, simply daily hygiene tasks. It's physically exhausting to take a shower, so I do wash with soap and water and wash the important parts. I feel gross taking a shower because I am just too exhausted to do it."*
Impact: IADLs	Female, 40–49	*"I would say pretty much 90% of my meals have all been take-out since COVID. I've hardly cooked anything just because it's been so difficult."*
Impact: Physical	Male, 30–39	*"I just couldn't really go to the gym, I couldn't do physical activity like that. I couldn't lift my daughter too much but I would try. But it was a combination of the two that really affected me the most."*
Impact: Emotional	Female, 50–59	*"It's hard to put a label on it because it's almost like a loss of sense of self. That's the best way I can put it into words. It's overwhelming, like feeling of loss and depression where it's not getting any better. Before, I had depression level come and go and now it's just staying with me."*
Impact: Social and leisure activities	Female, 30–39	*"So things like I used to... be very active in my church. I used to go every week multiple times, different events. I used to go out and hang out with friends. And those are things that I can no longer do. Not because of risk of catching COVID or something like that. But just because I physically don't have the ability."*
Impact: Professional	Female, 50–59	*"And like I said my job, I was going to attempt to work from home but my supervisor tells me oh everyone is back in the office now. I am not ready to get dressed in office clothes and drive to work and be on time. My extra income is just not... there. And it's hard. I've tried to find jobs that I can when I feel okay, but nobody is trying to do that."*

ADLs, activities of daily living; COVID-19, coronavirus disease 2019; IADLs, instrumental ADLs.

Figure 1. Literature review process for concepts related to symptoms and impact concepts

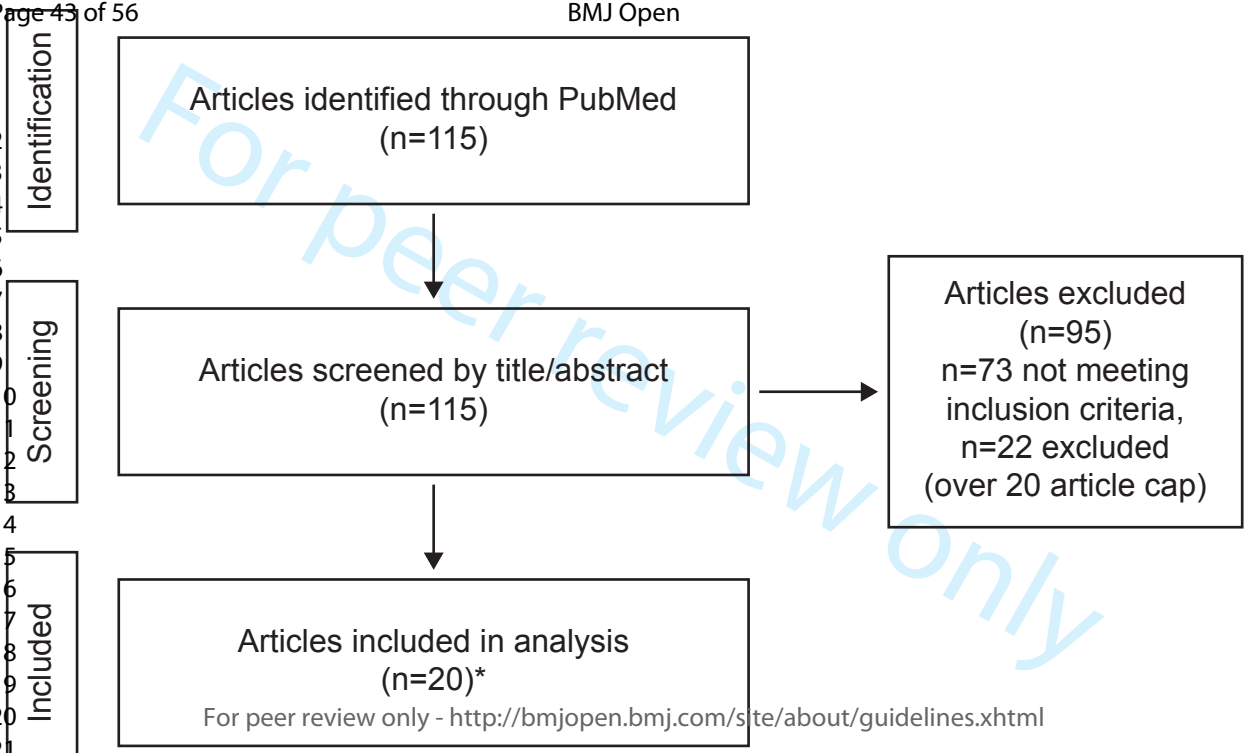
*It was decided *a priori* that the full text of up to 20 articles would be reviewed.

Figure 2. Detailed conceptual model describing the patient experience of long COVID-19

*Supported by patient interviews.

†Supported by clinician interviews.

‡Reported in literature.



Key

Domain	Domain
Sub-domain	Sub-domain

Symptoms

Upper respiratory tract

- Phlegm*,†,‡
- Runny nose and sneezing*,‡
- Sore throat‡
- Dry mouth*,‡

Lower respiratory tract

- Shortness of breath*,†,‡
- Cough*,†,‡
- Chest pain*,†,‡
- Difficulty breathing*

Smell and taste

- Altered or loss of taste*,†,‡
- Altered or loss of smell*,†,‡

Systemic

- Fatigue*,†,‡
- Weakness*,†,‡
- Joint pain*,‡
- Muscle aches and pain*,†,‡
- Body aches and pain*,‡
- Stiffness*
- Fever*,†,‡
- Chills*,†
- Hot flashes†
- Sweats*,†,‡
- Heart palpitations*,†,‡
- Changes to menstrual cycle*

Gastrointestinal

- Nausea*,‡
- Difficulty swallowing*
- Digestive problems (abdominal pain, bloating, diarrhoea, constipation)*,‡

Neuro-cognitive

- Numbness*,†,‡
- Pins and needles*,‡
- Ringing in ears*,†,‡
- Dizziness*,†,‡
- Lightheaded*,†
- Headache*,†,‡
- Haziness†,‡
- Confusion*
- Forgetfulness/ memory problems*
- Brain fog*,†,‡
- Concentration*,†,‡
- Difficulties finding the right word*,†,‡
- Challenges with fine motor skills*

Other

- Skin changes*,†,‡
- Red or dry eyes*,†,‡
- Vision changes*,‡

Impacts

Activities of daily living

- Eating*
- Drinking*
- Getting up from a bed or chair*
- Bathing*

Instrumental activities of daily living

- Household chores*,‡
- Child care*
- Challenges caring for pets*
- Cooking*
- Shopping*
- Loss of independence*

Physical impacts

- Sleep disturbance*,†,‡
- Need to nap*
- Exercise*,†,‡
- Ability to walk/climb stairs*
- Hair loss*,†,‡
- Decrease in Appetite and weight loss*,†,‡

Emotional

- Anxiety*,†,‡
- Depression*,†,‡
- Fear of reinfection*
- Frustration*,‡
- Heightened emotional responses*
- Irritability*
- Indifference*
- Not recognising oneself*
- (Post-traumatic) stress‡

Leisure/social

- Cautious about travel*
- Isolation*,‡
- Housebound*
- Feeling like a burden on families*,‡
- Engaging in fewer social activities*

Professional

- Ability to work full-time*,‡

Supplementary material

Supplementary methods

Process of patient recruitment by Rare Patient Voice and PRC Corporation

1. Recruiters invited potentially eligible patients to participate via email or telephone, using institutional review board-approved language.

2. Those interested in participating communicated with a trained recruiter via phone or email and confirmed whether they met the inclusion/exclusion criteria.

3. Patients were asked to provide verbal consent for their contact details to be provided to a Modus researcher and to participate in the study. Written informed consent was obtained electronically prior to patients' participation in the study. All patients were provided a copy of the fully signed consent form.

4. Patients were also asked to provide written confirmation from their clinician of their long coronavirus disease 2019 (COVID-19) diagnosis.

Screener form eligibility criteria

Inclusion criteria

- ≥18 years of age

- Clinically confirmed diagnosis of long COVID-19

- Initial COVID-19 infection must have been at least 180 days ago (documented via a positive polymerase chain reaction test)

- Currently experiencing long COVID-19 symptom(s) that cannot be explained by an alternative diagnosis
- The patient was not vaccinated at the time of the COVID-19 infection or 90 days thereafter
- The patient has received their last COVID-19 vaccination (including booster shot) at least 4 weeks prior to scheduling the interview
- Willingness and ability to participate in up to one 60-minute audio-recorded telephone or online interview in English
- Willingness and cognitive ability to provide electronic, informed consent
- Ability to speak, read, write and understand English
- Patient has any of the following risk factors for severe COVID-19:
  - Age ≥50 years
  - Obesity, defined as body mass index (BMI) ≥30 kg/m^2, or BMI (kg/m^2) ≥95th percentile for age and sex based on Centers for Disease Control and Prevention growth charts
  - Cardiovascular disease, including hypertension
  - Chronic lung disease, including asthma
  - Type 1 or type 2 diabetes mellitus
  - Chronic kidney disease, including those on dialysis

- Immunosuppressed (cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, or prolonged use of immune-weakening medications

Exclusion criteria

- Patient has concomitant illness(es) that in the recruiter or investigator's judgment would confound researchers' understanding and description of the long COVID-19 disease experience

Patient Information Collected

Patients' demographic information, including age, weight, height, sex, ethnicity, race, education level, employment status, occupation, living situation, marital status and household income, were collected. Comprehensive health information was also collected, including general health status at the time of interview, time since the beginning of COVID-19 symptoms, any hospitalisation due to COVID-19 and time since hospitalisation, smoking status, existing chronic disease or conditions, treatment with a monoclonal antibody, and COVID-19 vaccination status.

Saturation Analysis

Saturation refers to data adequacy, ie, the point at which no new relevant information emerges from additional qualitative data [1-3]. Within patient-reported outcomes research, saturation has been defined as "*the point in the data collection process when no new concept-relevant information is being elicited from individual interviews or focus*

groups, or no new information is deemed missing during cognitive interviewing" [4]. In the present study, the adequacy of the sample size was evaluated by a saturation analysis. Saturation analysis was conducted by grouping interviews chronologically and comparing the emerging sub-domains that reflected the conceptual categorisation of the codes. The sub-domains that emerged from the second quintile were compared with the sub-domains that emerged in the transcripts from the first. This comparison was repeated for each additional quintile. The cycle of data collection and analysis was continued until additional data collection produced no or minimal new information to further confirm or challenge the conceptual model.

Analysis

SAS software version 9.4 (SAS Institute, USA) was used for descriptive analysis. Continuous variables were described by their frequency, mean, standard deviation, median, first and third quartiles, extreme values (minimum and maximum values), and the number of missing values. Categorical variables were described by the frequency and percentage of each response choice, with missing data included in the calculation of the percentage.

Table S1. PubMed search strategy

Search	Term(s)	Results
1	Post-acute sequelae of SARS-CoV-2 infection OR long COVID-19 *Field: Title/Abstract*	134
2	Symptoms	7,204,054
3	Impact	1,262,676
4	Qualitative	325,386
5	Functioning	14,448,823
6	Health-related quality of life	445,770
7	1 AND 2 OR 3 OR 4 OR 5 OR 6	171
8	Filters: English, human participants	115

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S2. Overview of clinicians' backgrounds

Current position(s)	Specialty/training	Number of years practicing	Number of long COVID-19 patients treated per week
Attending physician at academic medical centre	Pulmonary and critical care	30	40
Private practice	General medicine	20	20
Attending physician in emergency department	Emergency medicine	15	Missing
Registered nurse at a hospital	Registered nurse	30	10–20
Registered nurse at a hospital	Registered nurse	26	Missing

COVID-19, coronavirus disease 2019.

Table S3. Saturation analysis of sub-domains: Symptoms

Group 1 (interviews 1–8) 24 concepts	Group 2 (interviews 9–16) 7 concepts	Group 3 (interviews 17–24) 7 concepts	Group 4 (interviews 25–32) 1 concept	Group 5 (interviews 33–41) 2 concepts
Altered or loss of smell	Chest pain	Digestive problems (abdominal pain, bloating, diarrhoea, constipation)	Difficulty swallowing	Challenges with fine motor skills
Altered or loss of taste	Dizziness	Skin changes		Stiffness
Body aches and pains	Dry mouth	Joint pain		
Brain fog	Fever	Lightheaded		
Chills	Vision changes	Decrease in appetite and weight loss		
Cough	Pins and needles	Muscle pain		
Difficulty breathing	Numbness	Changes in menstrual cycle		
Concentration	Fever			
Difficulties finding the right word				
Fatigue				
Hair loss				
Headache				
Heart palpitations				
Haziness				
Forgetfulness/ memory problems				
Nausea				
Phlegm				

Red or dry eyes
Ringing in ears
Runny nose
Shortness of breath
Sneezing
Sweats
Weakness

Table S4. Saturation analysis of sub-domains: Impacts

Group 1 (interviews 1–8) 10 concepts	Group 2 (interviews 9–16) 11 concepts	Group 3 (interviews 17–24) 1 concept	Group 4 (interviews 25–32) 0 concepts	Group 5 (interviews 33–41) 0 concepts
Anxiety	Sleep disturbance	Challenges caring for pets		
Depression	Bathing			
Childcare	Independently moving around			
Irritability	Feeling like a burden on families			
Cautious about travel	Housebound			
Cooking	Drinking			
Exercise	Eating			
Household chores	Fear of reinfection			
Isolation	Stress			
Engaging in fewer social activities	Shopping			
	Loss of independence			

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2. Strauss A, Corbin J. *Basics of Qualitative Research*. Thousand Oaks, CA: SAGE Publications, 1990.

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4. Rothman M, Burke L, Erickson P*, et al.* Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value Health* 2009;12:1075-83.

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	3–4
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	6–7
Purpose or research question - Purpose of the study and specific objectives or questions	7–8
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	9–10
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	9–10, Table 2
Context - Setting/site and salient contextual factors; rationale**	9–12, Tables S1
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	11
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	12
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	9–10

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	9–10
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	15, Tables 1 & 2
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	11–14
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	12–14, Tables S2 & S3
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	12–14

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	15–22
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	18–22

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	23–26
Limitations - Trustworthiness and limitations of findings	25, 5

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	28
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	28

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
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Thematic analysis to explore patients' experiences with long COVID-19: a conceptual model of symptoms and impacts on daily lives

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Abstract

Objectives: There is limited qualitative research on patients' experiences with long coronavirus disease 2019 (COVID-19), and how specific symptoms impact their daily lives. The study aimed to understand patients' lived experience of long COVID-19, and to develop a conceptual model representing the symptoms and their impact on overall quality of life.

Setting: Qualitative study consisting of a comprehensive literature review, and in-depth clinician and patient semi-structured interviews.

Participants: Forty-one adult patients with long COVID-19, of whom 18 (44%) were recruited through Regeneron Pharmaceuticals Inc.'s clinical trials and 23 (56%) through recruitment agencies; 85.4% were female and 73.2% were White. Five independent clinicians treating patients with long COVID-19 were interviewed. Concept saturation was also assessed.

Primary and secondary outcomes: Interview transcripts were analysed thematically to identify concepts of interest spontaneously mentioned by patients, including symptoms and their impacts on daily life, to guide development of the conceptual model.

Results: Findings from the literature review and clinician and patient interviews resulted in the development of a conceptual model comprising two overarching domains: symptoms (upper respiratory tract, lower respiratory tract, smell and taste, systemic, gastrointestinal, neuro-cognitive and other) and impacts (activities of daily living, instrumental activities of daily living, physical impacts, emotional, social/leisure activities

and professional impacts). Saturation was achieved for the reported impacts. The symptoms reported were heterogenic; neuro-cognitive symptoms, such as numbness, ringing in ears, haziness, confusion, forgetfulness/memory problems, brain fog, concentration, difficulties finding the right word, and challenges with fine motor skills, were particularly pertinent for several months.

Conclusion: The conceptual model, developed based on patient experience data of long COVID-19, highlighted numerous symptoms that impact patients' physical and mental wellbeing, and suggest humanistic unmet needs. Prospective real-world studies are warranted to understand the pattern of long COVID-19 experienced in larger samples over longer periods of time.

Word count: 297/300 words

Strengths and limitations of this study (up to five bullet points)

- This study included a comprehensive review of published literature related to long coronavirus disease 2019 (COVID-19), alongside in-depth, qualitative interviews with patients recruited from both clinical trials and healthcare research firms, as well as interviews with independent clinicians, to understand the patient experience of long COVID-19.
- While knowledge about acute COVID-19 symptoms and patient experience is relatively comprehensive, this study adds to the limited literature on the patient experience of long COVID-19 and its impacts on daily life, including neurocognitive, physical and emotional functioning.
- A limitation of this study is that the participants were predominantly White and female. Whilst the pathology of long COVID-19 is known to affect mostly women, it would be desirable to perform additional research in males and more diverse patient groups for better representation of the affected population.

Introduction

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), can experience long-term effects even if the virus is no longer detected with standard methods [1]. These effects are often referred to as "long COVID", "post-COVID-19 syndrome" or "post-acute sequelae of SARS-CoV-2" [2-4], and definitions may vary. According to the Centers for Disease Control and Prevention (CDC), patients with long COVID-19 continue to experience symptoms for ≥4 weeks after the initial infection with SARS-CoV-2 [1]. The National Institute for Health and Care Excellence (NICE) uses the term "post-COVID-19 syndrome" and defines it as "*signs and symptoms that develop during or after an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis"* [5]. While the World Health Organization (WHO) defines the condition as *"the illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within 3 months from the onset of COVID-19, with symptoms and effects that last for at least 2 months."* Similar to the NICE guidelines, the WHO specifies that *"the symptoms and effects of post COVID-19 condition cannot be explained by an alternative diagnosis"* [6].

The most commonly reported symptoms of long COVID-19 in current literature are fatigue, chest pain, muscle aches, persistent cough, fever, shortness of breath or difficulty breathing, loss of smell or taste, depression or anxiety, trouble speaking, memory, concentration and/or sleep problems [1, 6-10]. The CDC and NICE have indicated that long COVID-19 can affect anyone who has been infected, regardless of the severity of the initial infection [1, 5]. However, risk factors for long COVID-19 have

been reported to include female sex, older age and a history of more than five symptoms during the infection [11, 12]. Specific features of long COVID-19 have been identified via immune profiling, and include elevated humoral responses against SARS-CoV-2, and decreased levels of cortisol [13]. The reported prevalence of long COVID-19 ranges considerably, from 8% to 57% depending on the source and patient population evaluated [1, 14, 15]. A recent study reported an elevated risk of both hospitalisation and death during two years of follow up for patients who were hospitalised during acute COVID-19 infection [16]. While the exact prevalence of long COVID-19 is unclear, it is evident that management of patients with the disease poses a potentially significant burden for healthcare systems globally [17]. The health and economic consequences of long COVID-19 are predicted to be in line with acute disease; when calculating for a reduced quality-adjusted life expectancy, long COVID-19 has been estimated to cost around $2.6 trillion in the USA [18, 19].

Although COVID-19 is a global public health issue, and there is an increasing body of clinical and epidemiological literature on the incidence and prevalence of symptoms, to date there has been little empirical evidence directly from patients regarding the symptoms associated with long COVID-19 and how these symptoms impact their lives [7, 20-23]. Previously, we reported that the manifestation of symptoms in patients who were diagnosed with COVID-19 was heterogeneous and significantly affected all aspects of patients' lives; however, the study focused on patients with acute disease [24]. Due to its discrete characteristics, it is essential to understand and study long COVID-19 separately from acute COVID-19. We therefore sought to: (i) gain an in-depth understanding of the patient experience of long COVID-19 symptoms and the

impact on their daily lives; and (ii) understand the patient experience within the framework of a conceptual model based on empirical patient-relevant evidence informed by literature and patient and clinician interviews.

Methods

Literature review

Search strategy

An electronic search was performed on July 23, 2021, using PubMed to identify qualitative papers published up to that date that explored the patient experience of long COVID-19. A combination of search terms related to the target population were used, including (**Table S1**): post-acute sequelae of SARS-CoV-2 infection, long COVID-19, and patient experience (eg, symptoms, impacts). The search was limited to humans and English language publications. During the first stage of screening, articles were reviewed by title and abstract only. The second screening stage included full-text review of articles that were retained after the first screening. It was decided a priori that the full text of up to 20 articles would be reviewed.

Qualitative in-depth interviews with patients and clinicians

Patients

A purposive sample of patients was initially identified through Regeneron Pharmaceuticals Inc.'s clinical trial programme (COV-2066 in hospitalised participants [NCT04426695] and COV-2067 in non-hospitalised participants [NCT04425629]) [25, 26]. This patient sample was extended to the real-world through two independent healthcare research firms, Rare Patient Voice and PRC Corporation, which specialise in the recruitment of difficult-to-reach populations (**Supplementary Methods)**. Adults (aged ≥18 years) with a positive SARS-CoV-2 polymerase chain reaction test ≥180

days prior to enrolment into this study, experiencing long COVID-19 symptom(s) that could not be explained by an alternative diagnosis, and who were willing and able to participate in one 60-minute audio-recorded telephone or online interview in English, were included in the study. Full inclusion and exclusion criteria are provided in the **Supplementary Methods**, along with details of patient information collected.

Clinicians

Clinicians were eligible to participate if they were regularly seeing/treating more than five patients a week with long COVID-19 in the USA, and were willing to participate in a 60-minute audio-recorded telephone interview in English. Clinicians who only treated patients who resided in an institutional setting (eg, nursing home) were excluded. There were no pre-defined sample quotas set for the five clinicians; however, the recruitment process sought a diverse representation of professions (eg, general practitioners, nurses), specialties, and treatment settings (eg, hospital/non-hospital settings) where patients with long COVID-19 were regularly treated. A heterogeneous sample of five clinicians, who served as research consultants, was considered sufficient to obtain insights for input into the conceptual model.

Sampling

A purposive sampling approach was used and initially defined to target patients who were enrolled in Regeneron Pharmaceuticals Inc.'s clinical trials in the long COVID-19 sub-study in the USA. Additional recruitment of patients from external recruitment agencies were matched to the trial patients according to inclusion criteria. Due to the heterogeneity of both long COVID-19 symptoms and the affected population [27],

sampling covered a target population experiencing a range of symptoms. This ensured a diverse sample of up to 50 patients, which was estimated as an adequate sample size to reach conceptual saturation in the concepts of interest (COIs) [28, 29]. The sample size was anticipated to be adjusted downward based on recruitment feasibility and saturation analysis. In qualitative research, whether the sample size to obtain probable symptoms and impacts from a population is substantial or not is usually defined by the principle of data saturation (see below) [30]. The final sample size was to be determined by saturation based on good research practice [28, 31] and requirements by the US Food and Drug Administration (FDA) for establishing content validity [32].

Patient and clinician interviews

Semi-structured patient interview guides were developed in line with best practices outlined in the FDA patient-focussed drug development guidance [33]. The patient interview guides provided the researcher with a general outline for the semi-structured interview, but each interview was unique based on spontaneous patient responses to questions about symptoms and the impacts of long COVID-19 on daily activities and health-related quality of life (a copy of the patient interview guide is included in the **Supplementary Material**). Audio-recorded patient interviews were conducted via Microsoft Teams (use of camera optional by patient) by four experienced qualitative researchers who received specific training for this study, and who had backgrounds in psychology and anthropology as well as ≥2 years' experience in qualitative research. During the semi-structured interview, patients were asked open-ended questions to provide spontaneous inputs regarding the symptoms of long COVID-19 (experienced after the first 4 weeks of acute COVID-19). For example, 'Can you begin by telling me

about the symptoms you have experienced with long COVID-19? and 'How would you describe these symptoms in your own words?' and the impacts the symptoms had on the patients' daily lives. For example, 'In what ways has your day-to-day life changed since you began to experience long COVID-19 symptoms?' Specific questions for each reported symptoms were also asked, which included the symptom duration, as well as any changes over time such as improvement or worsening, and symptom severity over time. Additional questions asked for further descriptions of symptoms and which symptoms were the most and least bothersome. Emotional impacts, effects on social interactions and disruption to day-to-day life and activities were also explored. Examples of these questions are, 'How do your long COVID-19 symptoms affect your day-to-day life? And 'Are there day-to-day activities that you engage in differently since experiencing long COVID-19 symptoms?'. Additional questions on activities were to assess the patients' emotional wellbeing (e.g. anxiety or depression) and their ability to engage in physical activities and their usual exercise routine, to care for other people and pets, to spend time with others, to do their usual hobbies and to do grocery shopping.

Clinician interviews were also conducted by experienced qualitative researchers via Microsoft Teams. During the interview process, clinicians provided insights into patients' experiences of long COVID-19. All relevant findings extracted from the articles in the literature review and the clinician interviews were organised into a conceptual model to detail all potential COIs that could inform the patient experience of long COVID-19.

Ethical approval

All study documents (the protocol, interview guides, demographic and health information form, screener form and informed consent form) were approved by the Western Institutional Review Board-Copernicus Group Independent Review Board (IRB) before study initiation (IRB tracking # 20214272). Electronic informed consent was obtained from all patients. Patients were paid a fee in line with fair market value to cover the time taken to participate in the study.

Patient and public involvement

Patients and/or the public were not involved in the development, design, reporting, dissemination plans of this qualitative study. Patients were interviewed as part of the study. The results will be made available via publication.

Thematic data analysis

All interviews were audio recorded and transcribed verbatim. Transcripts from patient interviews were analysed thematically [34], using detailed line-by-line open and inductive coding [35-37] within ATLAS.ti software (Scientific Software Development GmbH). Coding was tailored to the research objectives of the study, which were the identification of symptoms and impacts of long COVID-19, including those spontaneously mentioned by patients as well as further probing of COIs. Codes and quotations were compared with the rest of the data and inductively categorised into higher-order overarching categories referred to as concepts, sub-domains and domains, reflecting their conceptual content underpinning. This categorisation was an iterative

process performed by a research team that involved comparison and cross-referencing between different analytic categories.

Saturation analysis

Details of the saturation analysis are provided in the **Supplementary Methods**.

Conceptual model

A conceptual model identifies and characterises COIs related to a health condition [38]. To develop a conceptual model of patient experiences with long COVID-19, data extracted from the literature review were inductively categorised into higher-order conceptual domains. Once coding was complete, a preliminary conceptual model was developed using the concepts extracted from PubMed; this was then revised with clinician input and further refined based on the results from patient interviews. Each concept was then considered and grouped into higher-order domains. If a concept was repeated across multiple sources, it was listed once. Ultimately, standard analytical techniques of conceptual model development were used to develop a visual representation of how the COIs relate to each other, grounded in a data-driven process based on patient-relevant empirical evidence [35-37, 39].

Analysis

Analysis details are provided in the **Supplementary Methods**.

Results

Literature review findings

The PubMed search of qualitative studies identified 115 abstracts for screening: 95 articles were excluded after abstract review and 20 full-text articles related to symptom and impact concepts were included in the final literature analysis (**Figure 1**). Articles presented symptoms at different conceptual levels (domain, sub-domains and concepts). Impacts were also presented at a high level of abstraction, eg, worsened quality of life.

Patient demographics and interviews

Interviews were conducted between 30 September 2021, and 12 May 2022. The study included 41 patients, of whom 18 (44%) were recruited through clinical trials and 23 (56%) through recruitment agencies (**Table 1**). The mean age was 53.6 years, 85% were female and 73% were White. The mean time between the start of any COVID-19 symptoms and the interview was 12 months (range: 1–25 months). Twenty-two patients (54%) received two doses of either the Moderna (27%) or the Pfizer/BioNTech (27%) vaccine, and 49% had been hospitalised. Most patients reported good (34%) or fair (37%) general health. At the time of the interview, hypertension/high blood pressure, arthritis, asthma, diabetes and mood disorders were self-reported by 18 (44%), 16 (39%), 10 (24%), nine (22%) and seven (17%) patients, respectively.

Clinician interviews

Participating clinicians included nurses and physicians who treated between 10 and 40 patients a week for COVID-19 (**Table S2**). All clinicians considered the CDC [1],

WHO [6] and NICE [5] guidelines (of ≥4 weeks after initially experiencing COVID-19 symptoms that cannot be explained by another condition) as the most appropriate timepoint for describing symptoms of long COVID-19, reasoning that they expected symptoms like cough to typically resolve after the acute phase of COVID-19 within this time frame.

Clinicians described fatigue, shortness of breath, chest pain/discomfort, cough, and loss of smell and taste as the most common symptoms experienced by patients with long COVID-19. In addition, they emphasised that long COVID-19 may affect any system of the body and that there was a wide variety of other, less common symptoms, such as headache, dizziness and hair loss. One clinician highlighted that many patients received a combination of treatments in relation to their symptoms, and that it became challenging to distinguish between less common symptoms related to long COVID-19 and the side effects of these treatments.

Clinicians reported that cognitive impairment accompanied common and less common symptoms, highlighting several mental health components such as depression, anxiety and feeling vulnerable. Additional impacts on quality of life included loss of appetite, sleep interruptions, lack of physical activity, inability to work and inability to perform activities of daily living (ADLs). Clinicians noted that most patients presented with ongoing symptoms from their initial COVID-19 diagnosis; of these, some presented cyclically. They also reported that a small number of patients who presented with severe respiratory symptoms were hospitalised, but most received care in outpatient settings. During the interviews, clinicians suggested that most symptoms would eventually resolve, though they found it challenging to say exactly when this would happen.

Conceptual model development and saturation

Data from the literature review and clinician/patient interviews yielded two overarching domains: symptoms and impacts. The refined conceptual model is presented in **Figure 2**. Information was added in the conceptual model about the source of concepts included (literature review, clinician interviews and/or patient interviews). All patient-reported concepts included in the model were reported by at least two patients.

Of the 41 symptoms presented, 93% were identified in the first 24 interviews (**Table S3**). In the remaining group of nine interviews, only two additional sub-domains were identified: challenges with fine motor skills, and stiffness. Stiffness added granularity to the body aches/pain sub-domain previously identified and, with the highly heterogeneous nature of long COVID-19, we can expect that additional symptoms would emerge with additional interviews. This indicated that the current analysis was comprehensive regarding the key symptom domains. For sub-domains in the impact domain, all unique sub-domains (n=22) were identified in the first three groups of the saturation analysis (**Table S4**). No new impacts emerged in the final 16 interviews. This indicated that saturation was achieved for the reported impacts.

Symptoms

Symptoms experienced after the first 4 weeks of acute COVID-19, as reported by patients, were elicited during patient interviews. Symptoms were grouped into seven domains: upper respiratory tract, lower respiratory tract, smell and taste, systemic, gastrointestinal, neurocognitive, and other. Due to the variation and complexity of symptoms experienced, the domains extended across specific areas of the body (ie,

upper respiratory tract) to more general subdomains (ie, weakness or aches in the systemic domain, not exclusive or specific to one area of the body). A selection of quotations covering these symptoms is presented in **Table 2** to reflect the broad and often debilitating nature of symptoms of long COVID-19 experienced by patients.

The upper respiratory tract domain reflected issues related to the sinuses and throat, and included symptoms such as phlegm, runny nose and sneezing, difficulty swallowing, and dry mouth. Difficulty in swallowing was described by one patient as like choking. The lower respiratory tract domain reflected issues related to the airways and lungs, and the sub-domains reflected symptoms such as shortness of breath, cough (including dry cough), difficulty breathing and chest pain. Loss of smell and taste was a commonly reported symptom in patients with long COVID-19. The severity of loss of senses varied widely, with some patients describing a total loss, while others reported that their senses were altered. The systemic domain included various symptoms which affected the entire body, rather than a single organ or body part, such as fatigue, weakness, heart palpitations, body aches, joint pain, fever, stiffness and chills. Fatigue was specifically described by patients in terms of its severity, whether it improved or not, and how variable the fatigue was. The gastrointestinal symptoms reported were nausea, diarrhoea vomiting, and other stomach-related issues. Many patients experienced neurocognitive symptoms such as brain fog, dizziness, memory problems, difficulties finding the right word, and challenges with fine motor skills. Brain fog reflected the challenges patients experienced to focus and stay on task. Neurocognitive symptoms were particularly pertinent for extended periods of times, with some patients reporting symptoms for several months.

Impact on daily life

The overarching domain “impacts” is defined by the activities and health-related quality of life experiences that patients report have been affected because of having long COVID-19. “Impacts” covered six sub-domains related to ADLs, instrumental activities of daily living (IADLs), physical impacts, emotional, social/leisure activities and professional impacts. A selection of quotations covering these domains is presented in **Table 3** to reflect the diverse and inconvenient negative impacts of long COVID-19 experienced by patients.

Quotations were categorized into ADLs if they referred to activities related to eating, drinking, getting up from a bed or chair, climbing stairs, and routines of self-care (eg, bathing). IADLs included activities related to household chores, taking care of children or pets, shopping and meal preparation. The physical impacts domain included sub-domains related to concepts associated with physical changes, such as changes to appetite and weight loss, hair loss and sleep disruption. It also included impacts on the ability to perform physical tasks such as walking and exercising. The emotional domain included sub-domains associated with changes in the patient’s psyche and mood in general, including issues associated with various worries and anxieties of having long COVID-19, depression, irritability, frustration, heightened emotional responses and not recognising oneself any longer. Activities related to social life, hobbies and leisure activities as well as sports and exercise were categorised under social and leisure activities. The professional domain captured changes in the patient’s ability to work.

Discussion

There is limited information on the patient experience of living with long COVID-19, and to our knowledge there is no current conceptual model that provides a visual representation of the symptoms and impacts of the disease. This qualitative study provides novel insight into the conceptualisation of the patient experience of long COVID-19. These rich patient qualitative insights are a useful resource to guide support and treatment requirements of those with long COVID-19 [40].

Following in-depth patient and physician interviews, we summarised the data captured in a simple and clinically grounded conceptual model comprising upper and lower respiratory symptoms, systemic symptoms, gastrointestinal symptoms, neuro-cognitive symptoms, altered or loss of smell and taste, and other symptoms. These symptoms were consistent with those reported by national and international health bodies such as the CDC [1], WHO [6] and NICE [5], and by systematic reviews [27, 41]. In addition to headache, dizziness and lightheadedness, which were also identified in the acute COVID-19 conceptual model [24], the long COVID-19 conceptual model included various neurocognitive symptoms such as numbness, ringing in ears, haziness, confusion, forgetfulness/memory problems, brain fog, concentration, difficulties finding the right word, and challenges with fine motor skills, and some of these symptoms were reported to be experienced for several months. Furthermore, while emotional concepts such as anxiety, depression, irritability and frustration were presented in the acute COVID-19 conceptual model [24], in the patients with long COVID-19 additional concepts included fear of reinfection, heightened emotional responses, indifference, not recognising oneself, and post-traumatic stress. At the time

our study was initiated, no other instruments were available to assess the impact of long COVID-19. Subsequently several instruments are now available. The modified COVID-19 Yorkshire Rehabilitation Scale, Symptom Burden Questionnaire for Long Covid, and post-acute (long) COVID-19 quality of life instrument each assess symptom burden in long COVID-19, but are not comprehensive in all symptoms identified in our model; particularly neurocognitive symptoms [42-44]. However, a handful of qualitative studies have demonstrated that patients with long COVID-19 report a very low state of mind and felt that their self-identity was affected, findings that are consistent with our own [21, 45]. Neuro-rehabilitation programmes for patients with long COVID-19 have proved helpful to improve working memory, verbal fluency and anxious-depressive symptomatology [46]. Our study further highlights the importance of understanding the impact these neurocognitive symptoms, which are not often reported during acute disease, can have on patients' emotional, social and professional lives.

In addition to symptoms, we also captured the impact of long COVID-19 and the changes in the daily lives of affected patients. The range of impacts due to long COVID-19 was consistent with those experienced during acute disease [24]; however, this study highlighted the emphasis on long-term impacts. A reduction in the number and/or severity of symptoms may mitigate the negative impact of long COVID-19 on patient health-related quality of life. Studies in populations with acute COVID-19 have shown that improvements in symptoms are correlated with improvements in outcomes and patient quality of life. However, additional qualitative and quantitative research is required to address this current knowledge gap, and further explore how management of symptoms in long COVID-19 could improve patients' lives.

Our study has two main limitations. First, the patients who were recruited from the external healthcare research firms closely matched the inclusion and exclusion criteria from the clinical trials. This approach may have resulted in a missed profile of patients with long COVID-19 who may be experiencing symptoms differently. Additional interviews with a broader exclusion and inclusion criteria could be considered as future research to determine whether they experience symptoms differently. Second, most of the patients in the present study were female and White. Nevertheless, this is consistent with other studies where the persistence of long COVID-19 symptoms for ≥12 weeks was higher in females than males [47]. There have also been reports on differences in prevalence of long COVID-19 symptoms in different ethnicities. One study that utilised data from community-based samples (>600,000) reported that an Asian population had a lower risk of persistent symptoms compared to a White population [47]. However, in other studies, Black Afro-Caribbean ethnic groups and other minority ethnic groups (native American, Middle Eastern or Polynesian) had a higher risk of long COVID-19 compared to a White population [12]. Additional studies are needed in different ethnic groups to fully understand the presentation and impact of long COVID-19 in different populations.

The present qualitative study provides unique and valuable insights on symptoms in patients with confirmed diagnoses of long COVID-19 and how it impacts their daily lives, including physical, emotional and psychological functioning. We found that patients typically experienced symptoms across of number of clinical domains during long COVID-19. Improving our understanding of the patient experience of the disease will help healthcare providers make informed decisions on optimised treatment options and

the support needed for patients to improve their overall health-related quality of life, while also easing the burden on patient's families and society [45]. Although no obvious symptomatic profiles were found during the interviews with patients, the heterogeneity of the symptom profiles should be further explored in longitudinal studies to aid in understanding any patterns in onset of symptoms, progression and possible long-term implications.

Conclusion

Our qualitative research reveals that long COVID-19 impacts all aspects of patients' daily life, particularly neurocognitive and mental health issues. To the best of our knowledge, this is the first study to report a conceptual model of long COVID-19 with neurocognitive and emotional concepts, based on empirical evidence from patient and clinician interviews. The model highlights, from a patient perspective, symptoms and impacts associated with long COVID-19, all of which showed significant negative effects on patient health-related quality of life.

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Competing interests

DR is a Regeneron Pharmaceuticals, Inc. employee/stockholder and former Roche employee, and current stockholder. SS-K, YZ, MH, TDN, and GPG are employees/stockholders at Regeneron Pharmaceuticals, Inc. JYC, and KP are employees of Modus Outcomes, and consulted for Regeneron Pharmaceuticals, Inc. AJP reported receiving personal fees from Regeneron Pharmaceuticals, Inc during the conduct of the study, personal fees from Imvaria, Boehringer Ingelheim, EBSCO/Dynamed, and Roche outside the submitted work. EM reports payments to his institution received from SciClone Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Pfizer, Chemic Labs/KODA Therapeutics, Cidara, and Leidos Biomedical Research Inc./NCI; and reports Advisory board: Basilea, and grants from NIH/NIAID, NIH/NIGMS, and BARDA.

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Author contributions

DR contributed to conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing (original draft, review, and editing). SS-K contributed to conceptualization, supervision, and writing (review and editing). JYC contributed to interview conduct, data curation, formal analysis, project administration, visualization, and writing (review and editing). KP contributed to interview conduct, data curation, formal analysis, project administration, supervision, visualization, and writing (review and editing). YZ contributed to operations, and writing (review and editing). MH contributed to conceptualization, supervision, and writing (review and editing). TDN contributed to operations, and writing (review and editing). AJP contributed to supervision, and writing (review and editing). EM contributed to supervision, and writing (review and editing). GPG contributed to conceptualization, supervision, and writing (review and editing).

Data availability statement

No additional data available.

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Table 1. Patient demographic and clinical characteristics

Variable	All (N=41)	Clinical trials (n=18)	Recruited (n=23)
Age, mean (SD)	53.56 (10.24)	56.44 (11.01)	51.30 (9.20)
Gender, n (%)			
Female	35 (85.4)	14 (77.8)	21 (91.3)
Male	6 (14.6)	4 (22.2)	2 (8.7)
Race, n (%)*			
White/Caucasian	30 (73.2)	12 (66.7)	18 (78.3)
Black/African American	9 (21.9)	4 (22.2)	5 (21.7)
American Indian/Alaskan	1 (2.4)	0 (0.0)	1 (4.3)
Asian	1 (2.4)	0 (0.0)	1 (4.3)
Other	2 (4.9)	1 (5.5)	1 (4.4)
Prefer not to answer	1 (2.4)	1 (5.5)	0 (0.0)
Self-reported health information at the time of the interview			
General health ratings, n (%)			
Excellent	3 (7.3)	2 (11.1)	1 (4.3)
Very good	3 (7.3)	3 (16.7)	0 (0.0)
Good	14 (34.1)	7 (38.9)	7 (30.4)
Fair	15 (36.6)	5 (27.8)	10 (43.5)
Poor	6 (14.6)	1 (5.5)	5 (21.7)
COVID-19 vaccination status, n (%)			
One dose of Pfizer/BioNTech	2 (4.9)	0 (0.0)	2 (8.7)
Two doses of Pfizer/BioNTech	11 (26.8)	5 (27.8)	6 (26.1)
Two doses of Moderna	11 (26.8)	8 (44.4)	3 (13.0)
One dose of Johnson & Johnson	1 (2.4)	0 (0.0)	1 (4.3)

Two doses of Pfizer/BioNTech AND a booster shot	3 (7.3)	0 (0.0)	3 (13.0)
Two doses of Moderna AND a booster shot	1 (2.4)	0 (0.0)	1 (4.3)
No COVID-19 vaccine received	12 (29.3)	5 (27.8)	7 (30.4)
Number and duration of symptoms, mean (SD)			
Time since symptoms began (months)	12.15 (5.87)	7.72 (2.11)	15.61 (5.53)
Number of symptoms reported per patient	7 (4.73)	6 (4.48)	8 (4.87)
Time between hospitalisation due to COVID-19 and interview (months)			
Not hospitalised, n (%)†	21 (51.2)	8 (44.4)	13 (56.5)
Mean (SD)	10.4 (4.95)	7.00 (6.67)	13.8 (5.05)
Self-reported comorbidities,‡ n (%)			
Hypertension/high blood pressure	18 (43.9)	5 (27.8)	13 (56.5)
Arthritis	16 (39.0)	7 (38.9)	9 (39.1)
Other§	19 (46.3)	6 (33.3)	13 (56.5)
Asthma	10 (24.4)	3 (16.7)	7 (30.4)
Diabetes (type 1, type 2, gestational)	9 (22.0)	3 (16.7)	6 (26.1)
Mood disorders (bipolar disorder, cyclothymia, etc.)	7 (17.1)	2 (11.1)	5 (21.7)
Cardiovascular disease (eg, heart failure, coronary artery)	5 (12.2)	0 (0.0)	5 (21.7)
Chronic obstructive pulmonary disease	5 (12.2)	2 (11.1)	3 (13.0)
Neurological conditions (eg, Parkinson's disease)	5 (12.2)	1 (5.5)	4 (17.4)
History of stroke	4 (9.8)	1 (5.5)	3 (13.0)
Cancer	2 (4.9)	2 (11.1)	0 (0.0)
None of the above	7 (17.1)	4 (22.2)	3 (13.0)

COVID-19, coronavirus disease 2019; SD, standard deviation.

*Patients could select more than one choice to reflect individuals with mixed race.

†Missing data included in calculation of percentages.

‡Patients could select more than one choice.

§Other refers to a comorbidity that was described only once and includes, but is not limited to, HIV/AIDS, multiple sclerosis, hypothyroidism, obesity, Hashimoto's disease, etc.

Table 2. Quotations from patients on the symptoms of long-COVID-19

Concept/Domain	Respondent demographics	Quotation
Symptom: upper respiratory tract	Female, 50–59	*"I would choke on it like a bread, cracker, peanut butter, anything – pudding even, pudding would get stuck. Anything that's thick it didn't go down easy. If it was liquidy [stet] I got it to go down. Oatmeal would get stuck. Just like it was stuck there, and I'd be choking on it."*
Symptom: Lower respiratory tract	Female, 40–49	*"So the coughing was... it felt the same as COVID. It was a dry cough. I couldn't stop. It'd be like cough and I'd try to talk and here I'd start coughing again."*
Symptom: Loss of smell and taste	Female, 40–49	*"Now the coffee to me is very sour and I have to use 4–5 sugars for that sourness in my taste buds to go away. I never had a sweet tooth but the coffee itself it tastes burnt to me, I can't have it black like I used to."*
Symptom: Systemic	Female, 50–59	*"Like, I literally could sleep all day and just lay there preferably sleeping. It just feels like I weigh 1000 pounds. I have no care for the things that need to get done. I don't care to eat; I don't care to work. I don't care... It's just a malaise, tiredness, and heaviness."*
Symptom: Gastrointestinal	Female, 30–39	*"I am having issues with digestion, appetite loss, I will have food that doesn't get digested well and just goes right through. Or I will have... issues with constipation so that's varying."*
Symptom: Neurocognitive	Female, 50–59	*"A fog comes over you and you can't think what you're trying to say. It's just hard to explain. It's a very weird feeling. You're sitting there speaking and all of a sudden you can't comprehend or concentrate to find the right words when you're trying to speak."*
	Female, 50–59	*"Very much so, I am dizzy a lot. Just going up and down the stairs. I live on the second floor. I have to hang onto the railing to make sure I am not going to fall. I have to concentrate on walking down the stairs. I have to concentrate on anything that I do that requires movement from me."*
	Female, 30–39	*"I've had a few severe situations with my memory. For instance, when I first started experiencing it, it's horrible that you're used to going and just driving, simple driving and knowing your way. For me being close to home and still forgetting how to get home,*

		not retaining that, because I am kind of new to the area but still it shouldn't have been an issue."
	Male, 50–59	*"Your recall is not as quick. Me trying to remember something I should remember… It comes back but it just isn't as quick, you have to wait a little while. It's not that you can't remember it's just that recall is slower."*
	Female, 50–59	*"Grabbing things and making sure I have a hold of them properly, otherwise I might not really be holding it… So I'll be smoking a cigarette and I'll go to take a puff of the cigarette and be like where did the cigarette go and it's fallen out of my hand and I didn't even know it."*

COVID-19, coronavirus disease 2019.

Table 3. Quotations from patients on the impacts of long-COVID-19

Concept/Domain	Respondent demographics	Quotation
Impact: ADLs	Female, 50–59	*"With the lack of energy, the fatigue, the shortness of breath when I am active, simply daily hygiene tasks. It's physically exhausting to take a shower, so I do wash with soap and water and wash the important parts. I feel gross taking a shower because I am just too exhausted to do it."*
Impact: IADLs	Female, 40–49	*"I would say pretty much 90% of my meals have all been take-out since COVID. I've hardly cooked anything just because it's been so difficult."*
Impact: Physical	Male, 30–39	*"I just couldn't really go to the gym, I couldn't do physical activity like that. I couldn't lift my daughter too much but I would try. But it was a combination of the two that really affected me the most."*
Impact: Emotional	Female, 50–59	*"It's hard to put a label on it because it's almost like a loss of sense of self. That's the best way I can put it into words. It's overwhelming, like feeling of loss and depression where it's not getting any better. Before, I had depression level come and go and now it's just staying with me."*
Impact: Social and leisure activities	Female, 30–39	*"So things like I used to... be very active in my church. I used to go every week multiple times, different events. I used to go out and hang out with friends. And those are things that I can no longer do. Not because of risk of catching COVID or something like that. But just because I physically don't have the ability."*
Impact: Professional	Female, 50–59	*"And like I said my job, I was going to attempt to work from home but my supervisor tells me oh everyone is back in the office now. I am not ready to get dressed in office clothes and drive to work and be on time. My extra income is just not... there. And it's hard. I've tried to find jobs that I can when I feel okay, but nobody is trying to do that."*

ADLs, activities of daily living; COVID-19, coronavirus disease 2019; IADLs, instrumental ADLs.

Figure 1. Literature review process for concepts related to symptoms and impact concepts

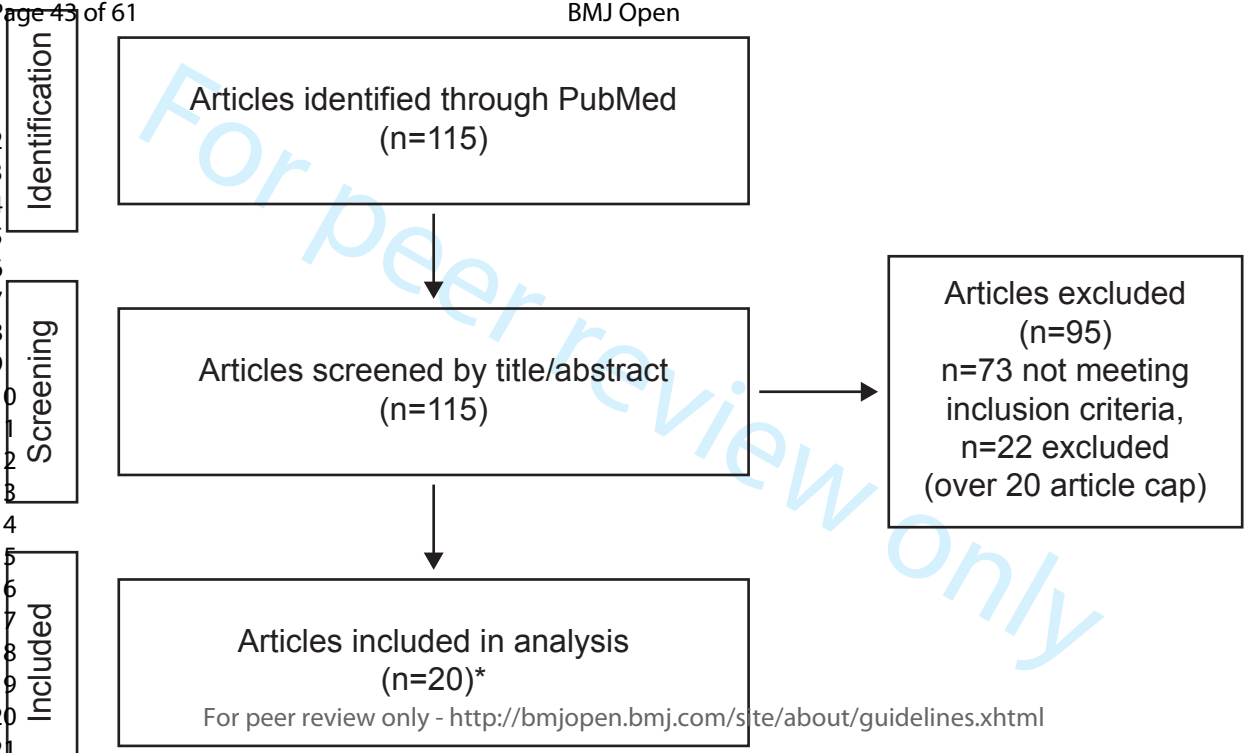
*It was decided *a priori* that the full text of up to 20 articles would be reviewed.

Figure 2. Detailed conceptual model describing the patient experience of long COVID-19

*Supported by patient interviews.

†Supported by clinician interviews.

‡Reported in literature.



Key

Domain	Domain
Sub-domain	Sub-domain

Symptoms

Upper respiratory tract
- Phlegm*,†,‡
- Runny nose and sneezing*,‡
- Sore throat‡
- Dry mouth*,‡

Lower respiratory tract
- Shortness of breath*,†,‡
- Cough*,†,‡
- Chest pain*,†,‡
- Difficulty breathing*

Smell and taste
- Altered or loss of taste*,†,‡
- Altered or loss of smell*,†,‡

Systemic
- Fatigue*,†,‡
- Weakness*,†,‡
- Joint pain*,‡
- Muscle aches and pain*,†,‡
- Body aches and pain*,‡
- Stiffness*
- Fever*,†,‡
- Chills*,†
- Hot flashes†
- Sweats*,†,‡
- Heart palpitations*,†,‡
- Changes to menstrual cycle*

Gastrointestinal
- Nausea*,‡
- Difficulty swallowing*
- Digestive problems (abdominal pain, bloating, diarrhoea, constipation)*,‡

Neuro-cognitive
- Numbness*,†,‡
- Pins and needles*,‡
- Ringing in ears*,†,‡
- Dizziness*,†,‡
- Lightheaded*,†
- Headache*,†,‡
- Haziness†,‡
- Confusion*
- Forgetfulness/ memory problems*
- Brain fog*,†,‡
- Concentration*,†,‡
- Difficulties finding the right word*,†,‡
- Challenges with fine motor skills*

Other
- Skin changes*,†,‡
- Red or dry eyes*,†,‡
- Vision changes*,‡

Impacts

Activities of daily living
- Eating*
- Drinking*
- Getting up from a bed or chair*
- Bathing*

Instrumental activities of daily living
- Household chores*,‡
- Child care*
- Challenges caring for pets*
- Cooking*
- Shopping*
- Loss of independence*

Physical impacts
- Sleep disturbance*,†,‡
- Need to nap*
- Exercise*,†,‡
- Ability to walk/climb stairs*
- Hair loss*,†,‡
- Decrease in Appetite and weight loss*,†,‡

Emotional
- Anxiety*,†,‡
- Depression*,†,‡
- Fear of reinfection*
- Frustration*,‡
- Heightened emotional responses*
- Irritability*
- Indifference*
- Not recognising oneself*
- (Post-traumatic) stress‡

Leisure/social
- Cautious about travel*
- Isolation*,‡
- Housebound*
- Feeling like a burden on families*,‡
- Engaging in fewer social activities*

Professional
- Ability to work full-time*,‡

Supplementary material

Supplementary methods

Process of patient recruitment by Rare Patient Voice and PRC Corporation

1. Recruiters invited potentially eligible patients to participate via email or telephone, using institutional review board-approved language.

2. Those interested in participating communicated with a trained recruiter via phone or email and confirmed whether they met the inclusion/exclusion criteria.

3. Patients were asked to provide verbal consent for their contact details to be provided to a Modus researcher and to participate in the study. Written informed consent was obtained electronically prior to patients' participation in the study. All patients were provided a copy of the fully signed consent form.

4. Patients were also asked to provide written confirmation from their clinician of their long coronavirus disease 2019 (COVID-19) diagnosis.

Screener form eligibility criteria

Inclusion criteria

- ≥18 years of age

- Clinically confirmed diagnosis of long COVID-19

- Initial COVID-19 infection must have been at least 180 days ago (documented via a positive polymerase chain reaction test)

- Currently experiencing long COVID-19 symptom(s) that cannot be explained by an alternative diagnosis
- The patient was not vaccinated at the time of the COVID-19 infection or 90 days thereafter
- The patient has received their last COVID-19 vaccination (including booster shot) at least 4 weeks prior to scheduling the interview
- Willingness and ability to participate in up to one 60-minute audio-recorded telephone or online interview in English
- Willingness and cognitive ability to provide electronic, informed consent
- Ability to speak, read, write and understand English
- Patient has any of the following risk factors for severe COVID-19:
  - Age ≥50 years
  - Obesity, defined as body mass index (BMI) ≥30 kg/m^2, or BMI (kg/m^2) ≥95th percentile for age and sex based on Centers for Disease Control and Prevention growth charts
  - Cardiovascular disease, including hypertension
  - Chronic lung disease, including asthma
  - Type 1 or type 2 diabetes mellitus
  - Chronic kidney disease, including those on dialysis

– Immunosuppressed (cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, or prolonged use of immune-weakening medications

Exclusion criteria

- Patient has concomitant illness(es) that in the recruiter or investigator's judgment would confound researchers' understanding and description of the long COVID-19 disease experience

Patient Information Collected

Patients' demographic information, including age, weight, height, sex, ethnicity, race, education level, employment status, occupation, living situation, marital status and household income, were collected. Comprehensive health information was also collected, including general health status at the time of interview, time since the beginning of COVID-19 symptoms, any hospitalisation due to COVID-19 and time since hospitalisation, smoking status, existing chronic disease or conditions, treatment with a monoclonal antibody, and COVID-19 vaccination status.

Saturation Analysis

Saturation refers to data adequacy, ie, the point at which no new relevant information emerges from additional qualitative data [1-3]. Within patient-reported outcomes research, saturation has been defined as "*the point in the data collection process when no new concept-relevant information is being elicited from individual interviews or focus groups, or no new information is deemed missing during cognitive interviewing*" [4]. In the present study, the adequacy of the sample size was evaluated by a saturation

analysis. Saturation analysis was conducted by grouping interviews chronologically and comparing the emerging sub-domains that reflected the conceptual categorisation of the codes. The sub-domains that emerged from the second quintile were compared with the sub-domains that emerged in the transcripts from the first. This comparison was repeated for each additional quintile. The cycle of data collection and analysis was continued until additional data collection produced no or minimal new information to further confirm or challenge the conceptual model.

Analysis

SAS software version 9.4 (SAS Institute, USA) was used for descriptive analysis. Continuous variables were described by their frequency, mean, standard deviation, median, first and third quartiles, extreme values (minimum and maximum values), and the number of missing values. Categorical variables were described by the frequency and percentage of each response choice, with missing data included in the calculation of the percentage.

Patient Interview Guide

Patient-centered outcomes research in long COVID-19 disease: Patient interview guide

Introduction

Before the interview begins, you should confirm the completion of the Participant Screener and Informed Consent Form for each participant.

Introduce yourself and the purpose of the study

Hello, my name is [Interviewer name] and I work for Modus Outcomes. Modus Outcomes is a company that talks to people about health various health conditions. Currently, we are working with a pharmaceutical company to find out more about your experience with long COVID-19. We define long COVID-19 as symptoms resulting from a COVID-19 infection that last longer than 4 weeks that are not explained by an alternative diagnosis. There are several symptoms you may suffer from, e.g., brain fog, fatigue or shortness of breath. There are many other symptoms, too.

Interview procedures including access to SE-LC19 using REDCap:

During this interview, you will have the opportunity to tell me about your personal experience with long COVID-19. I will ask you open-ended questions about the symptoms you experience and how those symptoms impact your life. After we discuss these questions, I will ask you to access the SE-LC19 weblink which you have received via email. I will ask you to provide me with your feedback on the questions you are required to answer.

The interview will last approximately 1 hour. You can stop this interview at any time, and it will have no impact on your compensation.

There aren't any "right" or "wrong" answers to the questions I will ask you today. We are really interested in knowing what YOU think about your long COVID-19 experience, so we appreciate anything you can tell us.

You will also be asked general demographic and health questions.

Audio recording

This interview will be audio recorded to make sure we capture all the information you share with us. Please try to speak clearly. If you need to take any breaks, please let me know. I can pause the recording at any time.

Anonymity and data handling

Audio recordings will be transcribed by an independent transcription agency. All information that could identify you will be left out of the transcriptions. These de-identified transcripts will be shared with the study sponsor and used in our analysis. Results of this interview will be anonymized, so no answers are attributable to any specific individual.

Adverse event reporting

If during the interview you happen to mention experiencing a medical event while receiving certain treatments developed by the study sponsor, we are required to report this to the company even if it has already been reported by you directly, your physician to the company, or the regulatory authorities. You will remain anonymous and only be identified by your participant ID number.

Closing

Do you have any questions for me?

Answer any questions that the participant may have. Ensure that they agree to have the interview audio recorded for the designated amount of time. Turn on the audio recording. Mention your name and the participant ID of the person you are interviewing along with the current date and time of the interview.

This is [Interviewer name] with participant [participant ID]. It is [date] at [time]. Do you agree to have this interview audio recorded? If *yes*, begin audio recording. If *no*, do not progress with interview.

Concept elicitation

Symptoms of long COVID-19

Can you begin by telling me about the symptoms you have experienced with long COVID-19? Please keep in mind that we are focusing only on symptoms that have lasted or appeared at least 4 weeks past your initial COVID-19 infection and are not explained by any other conditions you may be suffering from.

- What persistent symptom(s) did you notice?
- How would you describe those symptoms in your own words?

What symptoms have progressively disappeared after being persistent for more than 4 weeks?

Are there any other symptoms that have gotten worse over time? Please describe these symptoms.

What other new symptoms have you experienced since you have experience long COVID-19?

[If a clear description of symptom was not provided ask participant to describe the symptom:] What does the symptom feel like?

For each symptom:

How long have you experienced this symptom?

How has [symptom] changed since you first experienced it?

- In what ways has it improved/worsened/remained the same?

Does [symptom] change from day to day? During the course of the day? In what ways does it change?

Can you describe how severe [the symptom] is/was? Did the severity change since you were diagnosed?

Additional questions and probes:

Which symptom/s of long COVID-19 are most bothersome for you?

- Can you tell me more about [symptom mentioned]?
- Why is [symptom mentioned] more bothersome than others?

Which symptom/s of long COVID-19 are the least bothersome for you?

- Can you tell me more about [symptom mentioned]?

- Why is [symptom mentioned] less bothersome than others?

Impacts of long COVID-19 symptoms/diagnosis

How do your long COVID-19 symptoms affect your day-to-day life?

Can you describe to me what a regular/normal day was like for you *prior* to experiencing long COVID-19 symptoms?

- What did you do on a day-to-day basis during the period of COVID restrictions?

In what ways has your day-to-day life changed since you began to experience long COVID-19 symptoms?

- How does this compare to your 'normal' life before you experienced long COVID-19 symptoms?

Are there day to day activities that you engage in differently since experiencing long COVID-19 symptoms? Please note that we are interested in learning about any changes that are foremost due to suffering from long COVID-19 and not restrictions imposed due to the pandemic.

Why did you have to change how you engaged in these activities?

How has your life changed since you started experiencing long COVID-19?

How has your work been impacted by experiencing long COVID-19?

Which impacts/change bothers you the most and why? Which bothers you the least and why?

Which symptoms have affected your quality of life/daily activities the most? Why?

Examples for additional probes on broad activities:

- Ability to engage in physical activities such as exercise routines
- Emotional well-being (e.g. anxiety, depression)
- Caring for other people or your pets
- Household chores
- Doing your usual exercise routine (within the duration of the pandemic)
- Doing your usual hobbies (within the duration of the pandemic)
- Spending time with others (remotely or in person)
- Going grocery shopping to collect your medications or food

Which of your daily activities that were impacted by long COVID-19 have you been able to resume?

Closing and DHIF completion

Opportunity for participant to share additional information

Those are all the questions I have for you today. Is there anything else you want to tell me about your long COVID-19 experience that is important for researchers to know?

Follow up as appropriate.

Closing the interview

Thank you very much for helping us with this research. We appreciate your time and effort. The information you shared with us today will help researchers to learn about long COVID-19 symptoms and how best to measure them in the future. Findings and data from this research may be published so that the scientific community can learn more about long COVID-19 and how it affects people's lives. No personal identifiers will be included in any published material.

Conclude audio recording and close the interview. Ask participants the questions within the Demographic and Health Information Form (DHIF) and record their answers.

Table S1. PubMed search strategy

Search	Term(s)	Results
1	Post-acute sequelae of SARS-CoV-2 infection OR long COVID-19 *Field: Title/Abstract*	134
2	Symptoms	7,204,054
3	Impact	1,262,676
4	Qualitative	325,386
5	Functioning	14,448,823
6	Health-related quality of life	445,770
7	1 AND 2 OR 3 OR 4 OR 5 OR 6	171
8	Filters: English, human participants	115

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S2. Overview of clinicians' backgrounds

Current position(s)	Specialty/training	Number of years practicing	Number of long COVID-19 patients treated per week
Attending physician at academic medical centre	Pulmonary and critical care	30	40
Private practice	General medicine	20	20
Attending physician in emergency department	Emergency medicine	15	Missing
Registered nurse at a hospital	Registered nurse	30	10–20
Registered nurse at a hospital	Registered nurse	26	Missing

COVID-19, coronavirus disease 2019.

Table S3. Saturation analysis of sub-domains: Symptoms

Group 1 (interviews 1–8) 24 concepts	Group 2 (interviews 9–16) 7 concepts	Group 3 (interviews 17–24) 7 concepts	Group 4 (interviews 25–32) 1 concept	Group 5 (interviews 33–41) 2 concepts
Altered or loss of smell	Chest pain	Digestive problems (abdominal pain, bloating, diarrhoea, constipation)	Difficulty swallowing	Challenges with fine motor skills
Altered or loss of taste	Dizziness	Skin changes		Stiffness
Body aches and pains	Dry mouth	Joint pain		
Brain fog	Fever	Lightheaded		
Chills	Vision changes	Decrease in appetite and weight loss		
Cough	Pins and needles	Muscle pain		
Difficulty breathing	Numbness	Changes in menstrual cycle		
Concentration	Fever			
Difficulties finding the right word				
Fatigue				
Hair loss				
Headache				
Heart palpitations				
Haziness				
Forgetfulness/ memory problems				
Nausea				
Phlegm				

Red or dry eyes
Ringing in ears
Runny nose
Shortness of breath
Sneezing
Sweats
Weakness

Table S4. Saturation analysis of sub-domains: Impacts

Group 1 (interviews 1–8) 10 concepts	Group 2 (interviews 9–16) 11 concepts	Group 3 (interviews 17–24) 1 concept	Group 4 (interviews 25–32) 0 concepts	Group 5 (interviews 33–41) 0 concepts
Anxiety	Sleep disturbance	Challenges caring for pets		
Depression	Bathing			
Childcare	Independently moving around			
Irritability	Feeling like a burden on families			
Cautious about travel	Housebound			
Cooking	Drinking			
Exercise	Eating			
Household chores	Fear of reinfection			
Isolation	Stress			
Engaging in fewer social activities	Shopping			
	Loss of independence			

References

1. Morse JM. The significance of saturation. *Qualitative Health Research* 2016;5:147-49.

2. Strauss A, Corbin J. *Basics of Qualitative Research*. Thousand Oaks, CA: SAGE Publications, 1990.

3. Meyrick J. What is good qualitative research? A first step towards a comprehensive approach to judging rigour/quality. *J Health Psychol* 2006;11:799-808.

4. Rothman M, Burke L, Erickson P*, et al.* Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value Health* 2009;12:1075-83.

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	3–4
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	6–7
Purpose or research question - Purpose of the study and specific objectives or questions	7–8
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	9–10
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	9–10, Table 2
Context - Setting/site and salient contextual factors; rationale**	9–12, Tables S1
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	11
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	12
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	9–10

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	9–10
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	15, Tables 1 & 2
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	11–14
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	12–14, Tables S2 & S3
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	12–14

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	15–22
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	18–22

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	23–26
Limitations - Trustworthiness and limitations of findings	25, 5

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	28
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	28

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388