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Real World Cross-Sectional Analysis of COVID-19 Sequelae

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ABSTRACT

Background: An understanding of the sequelae following COVID-19 infection is continuously evolving. This retrospective cross-sectional analysis highlights persistent symptoms and quality of life in adult patients after hospitalization with COVID-19.

Materials & methods: Pandemic-induced lockdowns necessitated entirely virtual patient enrollment and follow-up. Participants completed telephone questionnaires on average 8-months after hospital discharge.

Results: N=95 participants completed the questionnaire. 62.4% were male and 37.6% were female, and the average age was 57 +15. Independently, those with gastrointestinal symptoms had 6.9 times higher odds of prolonged sequelae compared to those who did not have GI symptoms. No significant association existed between odds of recovery and use of over-the-counter medications or supplements.

Conclusion: Our findings support the burgeoning evidence surrounding the heterogeneity of post-COVID sequelae. Leveraging virtual technology, we gathered vital patient-reported information at a time of limited clinical experience.

Keywords: COVID-19; Pandemic; Cardiovascular; Neuropsychiatric

INTRODUCTION

The impact of the 2019 SARS-CoV-2 (COVID-19) virus cannot be understated. Worldwide, nearly 4 million people have expired after infection with COVID-19 as of July 2021.[1] Long-term sequelae of COVID-19, marked by persistent symptoms and ill health that remain far beyond the initial duration of infection from COVID-19, present significant and often prolonged morbidities-even in the face of an initially mild disease course.[2] An appreciation of the duration and type of symptoms experienced, impact on daily living, and quality

of life consequences resulting from COVID-19 infection is rapidly developing. Postacute syndromes have been well recognized in patients who have recovered from serious illnesses including viral infections. In addition, the clinical spectrum of COVID-19 infection severity may range between mild, moderate, critical, to extremely severe. Beyond the need to fill information gaps in post-COVID-19 complexities, pragmatic and innovative approaches to conducting research during a global pandemic must not be overlooked.

There is a limited understanding of why the SARS-CoV-2 infection lingers in some people and clears without any long-term effects in other individuals. At times, patients in the post-infectious stage may present with entirely different and more serious post-acute illnesses despite initially being asymptomatic during active infection. Ongoing collaboration between communities of patients, caregivers, researchers, clinicians, and advocates have been ongoing to shed light on this unrelenting and unpredictable post-COVID illness.[3] Chest pain, shortness of breath, muscle and joint pains, headaches, cognitive impairment, and fatigue are some of the most common symptoms that persist weeks or months after acute COVID-19 infection. The Centers for Disease Control and Prevention (CDC) offers the umbrella term “post COVID conditions" to describe ongoing symptoms more than 4 weeks from the first diagnosis of COVID-19 which is further categorized to include the designations of: 1) “long COVID,” 2) “multiorgan effects of COVID-19,” and 3) “effects of COVID-19 treatment or hospitalization”.[4]

As of July 2021, ten prior studies conducted in Europe, Asia, North America, and the Middle East have investigated long term symptoms and quality of life amongst COVID-19 patients after hospital discharge.[3,5-12] In these series of prior investigations, patients 18 years and older were called and offered the opportunity to complete telephone interviews or surveys between 1-6 months (average 4 months) post-discharge. Collectively, these reports characterized the most frequently reported symptoms in descending order as fatigue, joint pain, loss of taste/smell, and dyspnea.[13] Cardiovascular, neuropsychiatric, gastrointestinal and dermatologic systems were also notably impacted. Overall quality of life, disability, and physical activity have been included in prior reports, with multiple studies demonstrating notable decline following infection.[5,8,9,14] While initial reports suggested that severe respiratory symptoms were primarily driving COVID-19 hospitalizations, other investigations have associated hospitalization with vomiting, altered mental status, and dehydration, amongst other non-respiratory symptoms.[15,16]

Although researchers had begun exploring the use of modern technology to make face-to-face clinical trials virtually accessible long before the pandemic, COVID-19 posed unique challenges for the clinical research community.[17] Some investigators and hospital systems deemed it safe to deliver study medications directly to participants or proceed with in-person clinical study visits.18 Others, nonetheless, leveraged innovative, digital solutions to effectively support the COVID-19 clinical research landscape-harnessing the power of virtual study procedures and remotely collecting comprehensive, consistent, and reliable outcomes. Since post-COVID-19 sequelae can result after a mild course of disease, as well as after severe cases that require hospitalization for higher levels of care, conducting recruitment, consent, surveys, and follow-up virtually was crucial.

With the advent of the COVID-19 vaccine program and the evolving landscape of the disease course, clinicians are increasingly faced with the need to recognize, validate, and manage the long-term consequences of COVID.[19] Adapting our methodology to pandemic-driven practicalities, we collected real world longitudinal patient experiences for a significant duration post-hospital discharge highlighting symptom progression after acute

COVID-19 illness. By understanding the natural disease progression after acute COVID-19 and discerning the subsequent loss of health, clinicians can optimally support patients in their recovery.

METHODS

Study design & setting

This retrospective, observational, survey-based study was approved by the Scripps Office for Protection of Research Subjects and Institutional Review Board (IRB# 20-7573). The present results are reported according to the STROBE guidelines and the checklist can be found in supplementary Appendix B. This population of patients had at least moderate to severe symptoms requiring hospitalization. At the time of enrollment, this cohort of patients was healthy enough to be discharged home.

From May 2020 through April 2021, adult, English-speaking patients who tested positive for COVID-19 at a Scripps Health facility in San Diego County, CA, USA and were hospitalized between March 2020 to July 2020 for COVID-19 were called following discharge and asked if they would be willing to take part in a research study to help understand the long-term sequelae of COVID-19.

Participants

Study inclusion criteria consisted of a positive, real time, reverse transcriptase polymerase chain reaction (RT-PCR) upon admission for COVID-19 and documented COVID-19 infection during recovery. Patients who were pregnant, non-English speaking, limited in health literacy, or with an altered mental status when contacted via telephone were excluded from participation.

Patients were identified through an electronic medical record query and investigators solely called those patients who met the inclusion criteria. Information was obtained on 957 patients who had documented COVID-19 infection and were admitted to the hospital between March 2020 to July 2020. Of those, 648 were excluded and 319 were contacted for potential enrollment. A total of 95 participants consented and fully participated in the survey (Figure 1). All patients eligible to participate were at least 24 days past their COVID-19 diagnosis and were recovering in the outpatient setting. The average survey was conducted 252 days after confirmed COVID-19 diagnosis. Eligible patients were contacted by phone, and informed consent was obtained verbally.

Data collection

In-person contact with patients was not required as all data was collected virtually. All data and responses were stored in an electronic database built and stored securely in REDCap (Vanderbilt University, USA). The survey gathered symptom severity, interference with daily activities of living, and current health status as well as basic demographics, overall health, physical capabilities and use of pharmacologic remedies and natural supplements after hospital discharge. The list of symptoms, medications and impact on quality of life were refined per evolving recommendations by the CDC and prior similar studies involving post-discharge surveys.[4,5,11,19]

After obtaining consent to participate, subjects were asked the questions listed on the telephone survey tool. (see supplementary Appendix A - REDCap survey). Data on specific symptoms that may have been a consequence of COVID-19 infection were collected following each participant's acute COVID-19 infection. Participants were asked whether they experienced a range of 30 different symptoms before, during, and/or after their COVID-19 hospitalization, and if so, how many days each symptom persisted. Participants had an opportunity to disclose any symptoms or medications that were not on the standard list. Additional domains captured in the

telephone survey tool included use of tobacco products, marijuana use, over-the-counter medications, use of dietary supplements and vitamins either before, after, or before and after each participant had been hospitalized with COVID-19. Primary outcomes of interest were to discern which symptoms persisted after COVID-19 infection and which symptoms corresponded with full recovery at time of follow-up. Secondary outcomes of interest were to assess which patients took supplements or medications and whether that impacted the course of their illness.

The date when participants were called for potential study participation was recorded, and, if authorized by the participant, investigators tracked patient demographics, disease severity and date of diagnosis which was collected from the subjects' electronic medical records. After completion of data collection, our research team grouped symptoms classes into ten aggregated groups, and all analyses were conducted using these broader symptom classes (Table 1). Every effort was made to reduce biases in the study survey execution. The consent form and survey were read for each potential patient in the same way. Patients were given an opportunity to decline or ask questions of the investigator prior to agreeing to take the survey. Additionally, the patients were called in order of ascending medical record number, which prevented investigators from selecting patients in any order.

Statistical analyses

All analyses were performed using RStudio v. 4.0.3 (Boston, MA) and graphics were produced using GraphPad Prism v. 9.1.0 (San Diego, CA). All categorical data were described as both frequencies and percentages. Age was described by mean and standard deviation (SD) and follow up time after initial COVID-19 diagnosis was described as medians and interquartile ranges (IQR). Overall health-related data were described for all respondents, and symptom data was broken down into duration categories based on participants' responses. Medication and supplement use were similarly described by categories for timing of use (before, after, before and after). Univariable logistic regression was used to test each symptom class as an independent predictor (fixed effect) of whether a person would not be fully recovered at time of follow up, and odds ratios, 95% confidence intervals of odds ratios, and p-values were reported. To test for conditional associations, all symptom classes were included as fixed effects in a multivariable model for the outcome of not being fully recovered, and the model was reduced in a backwards stepwise approach. Each of the supplements and medications was also tested as independent fixed effects in univariable logistic regression for independently predicting making a full recovery. All p-values reported are two-tailed and a $p<0.05$ was considered statistically significant. If the patients permitted the investigators to view their medical record, data was extracted from the medical record to obtain demographic information; otherwise, this data was missing from our analyses and reported as such.

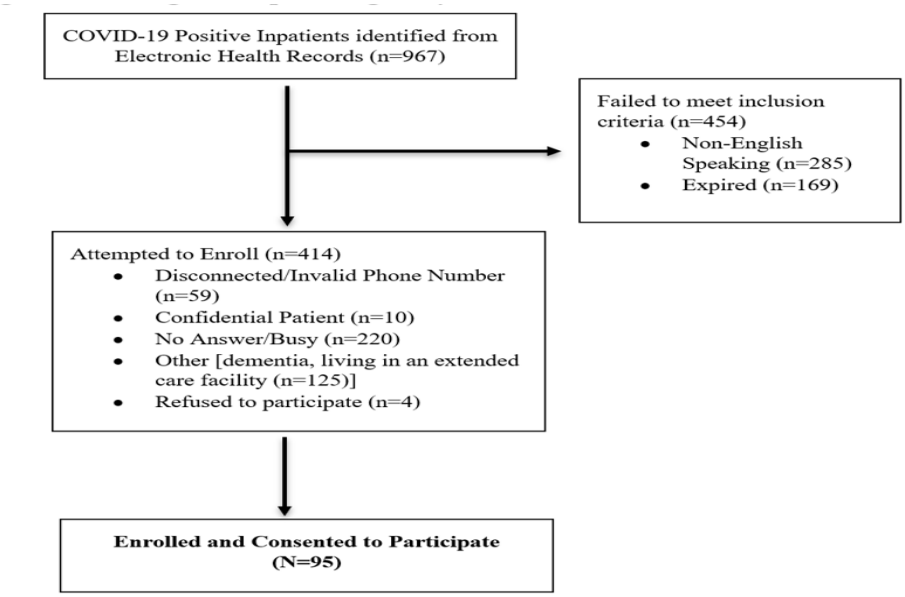

Figure 1: Flow diagram detailing participant eligibility and enrollment.

Table 1: Symptom classification.

Generalized	**Gastrointestinal (GI)**	**Breathing**	**Muscle/Joint**	**Neurological**
Fever Chills Night sweats	Unusual abdominal pain Nausea Vomiting Skipping meals Diarrhea	SOB w/ exercise or exertion Breathlessness	Strong muscle aches Joint aches Body pain	Headache Lightheadedness Dizziness
Upper Respiratory Infection (URI)	**Loss of Taste/Smell**	**Cardiac**	**Sleep/Fatigue**	**Skin/Hair/Nails**
Runny nose Cough Sore Throat	New loss of taste smell Loss of smell / taste	Palpitations Chest Pain Chest tightness Decreased exercise tolerance	Unusual fatigue Difficulty sleeping	Hair loss Discolored toes/fingers Sores/rash on hands/feet

RESULTS

From July 2020 to April 2021, N=319 patients were contacted for the study, of which 95 patients agreed to participate. The average age and standard deviation of the participants was 57+15 years old, and over half were white (59.1%) males (62.4%). (Table 2) The median elapsed time from COVID-19 diagnosis to the time of this survey was 252 days (IQR 191-295 days).

Table 2: Participant Demographics (N=95)

Demographics	N (%)
Age, years ± SD	57 ± 15
Male sex	58 (62.4)
Race	
White	55 (59.1)
Asian	10 (10.8)
Unknown/Other	22 (23.7)
Black	8 (8.6)

For the primary outcome of interest, 94% of participants reported persistent symptoms of COVID-19 infection. These symptoms were categorized into ten symptom types (Table 1). The most common symptoms were fever/chills/night sweats, gastrointestinal symptoms (diarrhea, nausea, and vomiting), shortness of breath, fatigue, and difficulty sleeping (Figure 2).

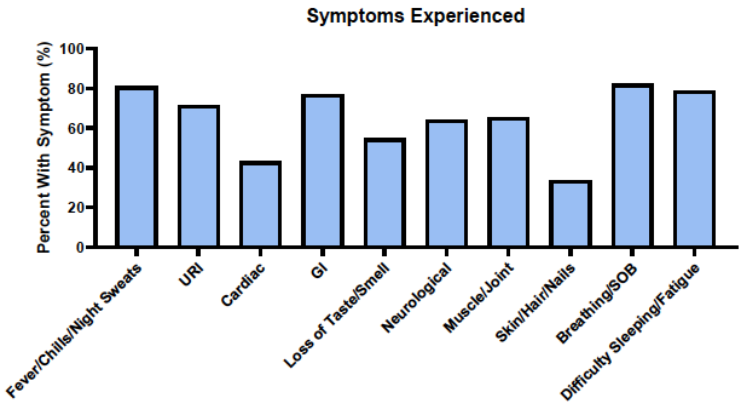

Figure 2: Prevalence of symptoms experienced stratified by system.

The longest lasting symptoms were hair loss and fatigue (Figure 2). Hair loss occurred in 24.2% of patients and persisted for over 20 days in the majority of participants. Other predominantly persistent conditions included sores or rashes on hands and feet, decreased exercise tolerance, shortness of breath upon exertion, discoloration of toes or fingers, unusually hoarse voice, and joint aches. As a category, fever/chills/night sweats were experienced for the shortest time, with only 12% of participants experiencing these symptoms beyond 20 days. Among those respondents without full recovery from symptoms at time of survey completion, the most common persistent symptom was unusual fatigue, followed by shortness of breath and decreased exercise tolerance.

The majority of participants conveyed that their daily activities of living were severely impacted as a result of their prolonged symptoms (Figure 3). Overall, 43% of patients at the time of completing the questionnaire had not completely recovered from their array of symptoms-all of which had not been present prior to COVID-19 infection (Table 4).

Independently, having loss of sense of taste and/or smell, symptoms involving skin, hair, and/or nails, and GI symptoms were each associated with increased odds of not fully recovering from COVID-19 by time the survey was conducted relative to those who did not have each of those symptoms, respectively. To test for conditional

associations, all symptoms were tested in a multivariable model, and following a backwards stepwise approach, only the presence of GI symptoms was significantly associated with not fully recovering from COVID-19 by the time of survey (see Figure 4). Notably, those who reported GI symptoms were 6.9 times less likely to fully recover relative to those who reported no GI symptoms.

For the secondary outcome, 91.6% of patients were taking supplements around the time of their COVID-19 infection, and 85.3% of patients were on no supplements at the time of their COVID-19 infection. The most common supplement taken after COVID-19 infection was Vitamin D (Figure 5). None of the dietary supplements, vitamins, or medications had greater or lesser likelihoods of predicting a full recovery or decreasing the symptom burden after COVID-19 infection. Numerically, a greater percentage of participants who took zinc after COVID-19 infection experienced fewer persistent symptoms and were more likely to recovery (58% vs 43%), although this association was not statistically significant. Nonetheless, participants were significantly more likely to try new dietary supplements, vitamins and minerals after infection with COVID-19 compared to beforehand. Since the present study was not a randomized controlled trial with a separate control group, we do not have sufficient evidence to conclude whether zinc supplementation and/or loss of initial taste and smell was associated with greater odds of full recovery.

Following the initial questionnaire, patients had the opportunity to disclose any additional symptoms and those reported included the following: Orthopedic changes (pain/weakness/paralysis) (n=18); Altered mental status (anxiety/depression/dementia/disorientation) n=13; Balance loss or syncope (n=6); Skin/nail changes (n=5). In total, a greater proportion of participants (57%) had not fully recovered at the time of the survey's administration.

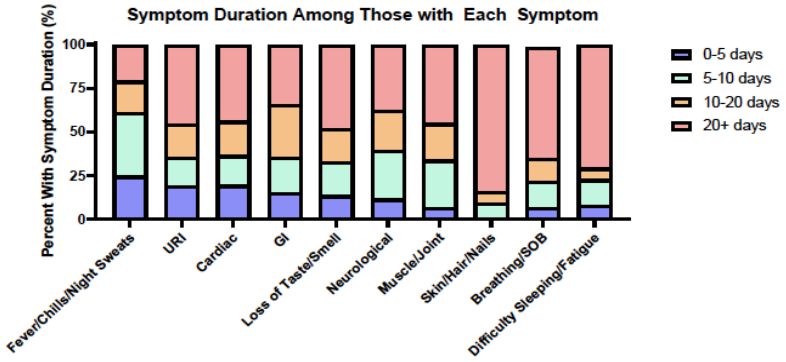

Figure 3: Symptom duration among aggregated symptom groups.

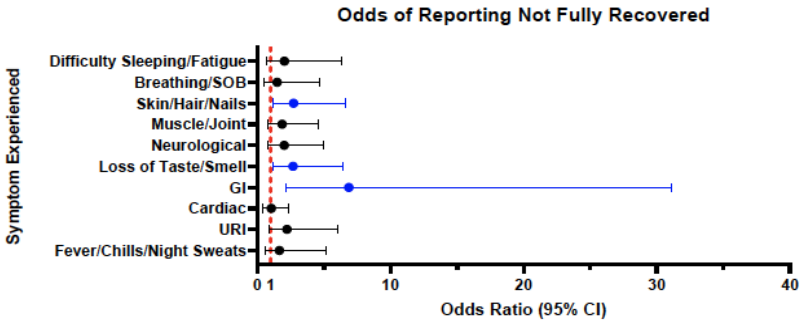

Figure 4: Odds of prolonged recovery by symptoms experienced.

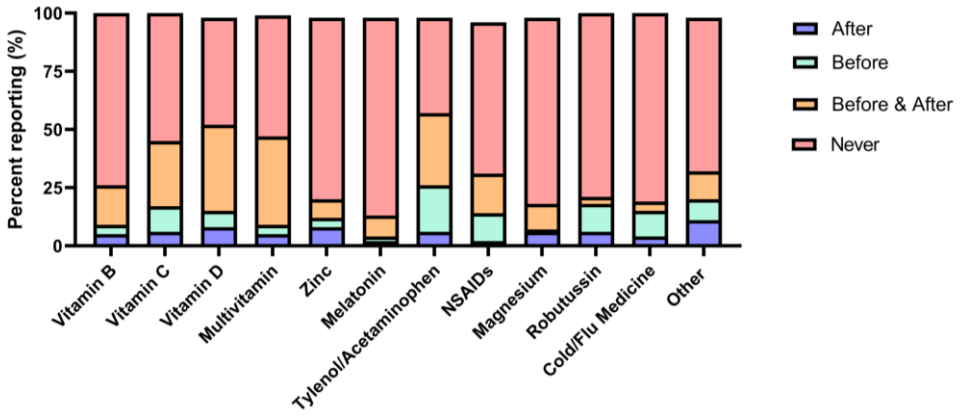

Figure 5: Timing of medications taken.

DISCUSSION

Many unknowns remain regarding post-COVID-19 illness, but the biomedical community is amassing evidence regarding mechanisms, risk factors, therapies, and disease outcomes. COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations. Our study highlights the heterogeneity of responses after COVID-19 by gathering personalized reports from patients hospitalized for COVID-19 infection. Not every patient reported having upper respiratory symptoms, and this study reinforces the heterogeneity of presenting symptoms and the importance of a broad focus in characterizing COVID-19 and post-COVID-19 sequelae. The existing literature has demonstrated that patients with post-COVID-19 lingering symptoms experienced varying levels of disease severity ranging from those who were able to remain at home to those who required protracted intensive care.[20,21] Notably, at the time of survey of all participants in this study, each participant was in an outpatient setting. It is important to recognize that all participants in the present study experienced symptoms severe enough to warrant inpatient hospitalization, but not all patients suffered from persistent symptoms beyond the normal disease course. While it was initially surprising to learn from the literature that even asymptomatic patients could go on to have long term sequelae, our study highlights that being hospitalized for COVID-19 does not necessarily mean that long COVID is inevitable. While all participants were contacted in their homes, rates of post-discharge facility needs (e.g., Skilled Nursing Facilities, Hospice, public health quarantine facilities, etc.) vary widely in existing literature and will require additional investigation to inform appropriate resource preparation and decisions on post-acute care transitions.[22-24]

The finding that patients continued to display symptoms several months after their initial diagnosis speaks to the chronicity of several COVID-19 related symptoms and further supports patient reports and additional research on what is described as “COVID-19 long haul”.[25] It is important that clinicians, researchers, and caregivers validate the patients’ experiences of these burdensome symptoms that may be result after COVID-19. The significantly high prevalence and low resolvability of fatigue in these patients is unfortunately a prominent feature of post-COVID-19, which may contribute to increased healthcare utilization, poor quality of life, and overall greater rates of disability in the long run.[26] The present findings supplement the existing evidence of the natural disease course, an understanding of which will be the foundation for future systems based management.

Numerous studies demonstrate the extensive heterogeneity in symptoms experienced after COVID-19. This study found that initial GI symptoms during the acute COVID-19 course were significantly associated with not fully recovering by time of follow up. Patients with GI symptoms had similar median time of follow-up as compared to those without GI symptoms. Of note, observational studies found a stepwise increase in the likelihood of worsened outcomes depending on the number of initial GI symptoms experienced.[29] Patients with post-COVID-19 sequelae have also demonstrated increased risk of prescription medications, as well as increased risk of death.30 Additional study is warranted to understand whether there are relationships between severity or duration of initial GI symptoms and long-term COVID-19 outcomes, and prospective study of patients experiencing such symptoms would be informative.

The loss of smell and taste in these patients has been a notable deviation from previous coronavirus infection syndromes and may be reflective of zinc deficiency. Patients with zinc deficiency have demonstrated worse survival rates after COVID-19 infections, and zinc supplementation supported recovery of smell and taste among post-COVID-19 patients.[28] Among patients in our study who experienced loss of smell or taste, while not significant, zinc supplementation was modestly more frequent among those who had symptom recovery, though prospective study is needed to better elucidate whether this relationship is robust.

A unique aspect of this study is that it was entirely virtual. The project was completed without requiring participants to report to the hospital or office. This factor enabled investigators to capture longitudinal, anecdotal reports during a time months after their initial COVID-19 diagnosis. Many patients are still afraid to participate in clinical research as they are concerned with potential COVID-19 exposure from returning to the healthcare facility many times for follow up and study visits. Other patients are unable to make visits due to lack of transportation, work conflicts or family obligations. This research study serves as a model for clinical trial conduct that allows a broader population outreach. There is much valuable information that is not captured in the medical record where, oftentimes, a chart review misses or oversimplifies the patient reports.

Limitations of the study methodology include the possibility of recall bias, reliance on patient recollections of acute symptoms in the midst of the recovery phase, and the subjective rating of symptoms. Prospective studies are warranted to reduce potential biases. Patients were required to have a personal phone in order to participate in the survey remotely and were only called once without multiple attempts by researchers. Given the previous evidence that COVID-19 disproportionately affects minority populations, future studies should seek to include greater diversity, non-English speaking participants, and marginalized populations.[31]In terms of sample limitations, this may have induced inclusion bias of participants who had the flexibility to talk during the business day. Limitations in data availability included the potential for undetected pre-COVID-19 abnormalities and lack of control for comorbid conditions across participants based on their post-COVID-19 symptomatic experiences. We also did not assess how long participants were hospitalized for both COVID-19 and/or other pre-existing diseases. Although all of these patients were hospitalized for acute COVID-19 infections, additional studies ought to evaluate whether less severe, non-hospitalized patients experience sequelae of different types or duration after COVID-19. Data regarding patient demographics and clinical history were not analyzed for this study but are being analyzed as part of a future longitudinal study. Limitations of the study methodology include the possibility of recall bias and the subjective rating of symptoms. Another source of biased is that patients had to be able to complete the survey in English. If they did not speak English or if the investigator was not certain

that they understood what the survey was asking them they were excluded from the study. Also, the participants needed to have a working phone and the time to take the survey. This potentially led to unintentional exclusion of people that had no working phone, were homeless, financially disadvantaged, living in care facilities or worked in a job that did not permit phone calls. Of contemporary importance, it should be noted that patients in this study had diagnosis dates from March to July 2020 before there was widespread prevalence of newly emerging variants of COVID-19 and it is unknown whether the post COVID sequalae remain consistent with these newer strains.

Participant-centered, subjective reports are invaluable during a time when patients may feel isolated and burdened by prolonged symptoms after COVID-19 hospitalization. Gathering valuable qualitative information virtually via the approach employed in this study has great potential to spur additional investigations on pathophysiological drivers of these burdensome sequelae and longer-term outcomes. Tools such as the Post-COVID-19 Functional Status Scale will enable frequent and valid assessments of persistent COVID-19 symptoms in a systematic fashion.[32] Wearable devices also permit continuous tracking of an individual's physiological and behavioral metrics before infection, during the course of active COVID-19, and throughout prolonged recovery periods to baseline.[33] Nonetheless, ongoing research is warranted to understand the mechanisms underlying these long-term sequelae. The preliminary and descriptive results of this study further illuminate the need for continuous and comprehensive care of patients with SARS-CoV-2 infection after hospital discharge.

CONCLUSION

This pragmatic, fully virtual observational study of prolonged COVID-19 sequelae demonstrates the varied experiences of patients suffering from persistent symptoms post-COVID-19 infection. Patients with gastrointestinal symptoms were significantly more likely to experience prolonged sequelae. Supplement therapy did not appear to impact risk of prolonged symptoms. Further research to help guide management of prolonged COVID-19 symptoms is needed.

Beyond the real-world experience and filling information gaps in post-COVID-19 complexities, the true value of this study is the pragmatics and lessons learned from conducting research during a global pandemic. This study provides a demonstration that investigators can leverage virtual technology to best understand and validate patient experience and answer patient centered questions and gather patient reported outcomes to meaningfully manage patients during a pandemic when information is limited. Future trials may benefit from similar methodology.

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