

Patients with uncomplicated COVID-19 have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic

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Abstract:

To assess the prevalence of persistent functional impairment after COVID-19, we assessed 118 individuals 3-4 months after their initial COVID-19 diagnosis with a symptom survey, work productivity and activity index questionnaire, and 6-minute walk test. We found significant persistent symptoms and functional impairment, even in non-hospitalized patients with COVID-19.

Keywords: COVID-19, SARS-CoV-2, Long Covid, functional impairment, COVID-19 symptoms

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Introduction

To date, >25 million Americans have been diagnosed with SARS-CoV-2.¹ Most infections are mild/moderate with 8-15% of patients requiring hospitalization². In mild cases, two-thirds return to baseline after a median of 7 days.³ However, symptoms can persist months after infection. “Long COVID” has been reported in 87% of hospitalized patients two months post-infection⁴ and in 53% of non-hospitalized patients 125 days after diagnosis.⁵ The most common persistent symptoms are fatigue, hyposmia/dysgeusia, dyspnea, arthralgias, and myalgias.⁴⁻⁶ The degree of impairment in “Long COVID”, or if long-term symptoms are equally prevalent in hospitalized vs. non-hospitalized COVID-19 patients, is unknown.

This study compared ongoing symptoms and functional impairment in hospitalized vs. non-hospitalized COVID-19 patients.

Methods

Patients recruited after PCR-confirmed COVID-19 infection were invited to return for long-term follow-up visits 3-4 months post-COVID-19 diagnosis. The majority were enrolled in clinical trials at Stanford at disease onset including trials of Peginterferon-lambda (NCT04331899) or Favipiravir (NCT04346628) in non-hospitalized patients, and the Gilead SIMPLE trial (NCT04292899) for hospitalized patients. Patients were then enrolled in one of two long-term follow-up studies: Peginterferon-lambda’s optional long-term follow-up and the IRIS Study which recruited a convenience sample of hospitalized and non-hospitalized patients at Stanford who agreed to participate after being contacted by IRIS’s Study Coordinator. At follow-up, a detailed medical history including comorbidities, targeted physical exam, survey of symptoms present at time of follow-up, Work Productivity and Impairment (WPAI) questionnaire, and 6-minute walk test were

completed. These protocols were approved by the Stanford Institutional Review Board. Participants provided written informed consent.

We used Chi-square, Fischer's exact and independent samples t-tests to compare characteristics of hospitalized vs. non-hospitalized patients. Outcomes assessed at follow-up were 1) presence of ≥ 2 symptoms, 2) any activity impairment, and 3) percent of expected distance achieved on 6-minute walk test.⁷ Logistic and linear regression models examined factors associated with these outcomes.

Results

As of November 2020, 118 patients completed follow-up visits a median of 119.3 days after initial COVID-19 diagnosis. Overall, twenty-two (18.6%) were hospitalized for a median of 7.5 days (IQR 5-16); of these, 11 (55%) were admitted to the ICU and 6 (27%) were intubated. Hospitalized patients were more likely to be older, non-white, and have comorbid medical conditions than non-hospitalized (Table 1). At COVID-19 onset (date of first positive test), most prevalent symptoms were fatigue (85.6%), cough (74.6%), loss of taste/smell (74.6%), and fever/chills (62.7%). Fever/chills (95.5% vs 55.2%, $p < 0.001$) and dyspnea (50.0% vs 21.1%, $p < 0.001$) were more prevalent in hospitalized patients vs. non-hospitalized patients.

At 3-4 months post-COVID, 81.8% of hospitalized and 64.2% of non-hospitalized patients, had any symptoms ($p = 0.11$). The most prevalent symptoms at 3-4 months post-COVID-19 follow-up in both hospitalized and non-hospitalized patients included fatigue and dyspnea; dyspnea was more common in hospitalized vs. non-hospitalized patients ($p = 0.006$, Table 1). In univariate analysis, cough (odds ratio (OR) 2.58 [1.08-6.15], $p = 0.033$), dyspnea (OR 3.45 [1.61-7.38], $p = 0.001$), and sore

throat (OR 2.10 [1.00-4.43], $p=0.049$) at COVID-19 onset were significantly associated with odds of having ≥ 2 symptoms at 3-4 months post-COVID-19. In multivariate analysis adjusting for gender, age, race/ethnicity, hospitalization status, and BMI, only dyspnea at onset was associated with significantly higher odds of ≥ 2 symptoms at follow-up (aOR 3.70 [1.51-9.08], $p=0.004$, Supplemental Table 1).

On univariate analysis, older age (OR 4.15 comparing >55 to <35 years [1.36-12.65], $p=0.012$), and hospitalization (OR 3.29 [1.09-9.93], $p=0.035$) were associated with higher odds of any activity impairment at 3-4 months follow-up. Presence of dyspnea (OR 2.51 [1.15-5.49], $p=0.021$) or fatigue (OR 7.80 [1.65-36.85], $p=0.010$) at COVID-19 onset were also associated with long-term activity impairment. Only presence of fatigue remained significant in multivariate analysis (OR 6.03 [1.04-34.87], $p=0.045$) after adjusting for gender, race/ethnicity, age, BMI, and hospitalization status (Supplemental Table 2).

Finally, we assessed patient's functional status through the 6-minute walk test. In univariate analysis, hospitalization at onset (coef. -5.99 [-11.4-{-0.57}], $p=0.031$), LatinX ethnicity (coef. -10.84 [-15.1-{-6.6}], $p<0.001$), higher BMI (-0.65 [-0.96-{-0.34}], $p<0.001$), ≥ 1 comorbidity (-4.79 [-9.33-{-0.25}], $p=0.039$), and having fevers/chills (-4.82 [-9.23-{-0.42}], $p=0.032$) or cough (-4.99 [-9.91-{-0.06}], $p=0.047$) at onset were associated with achieving lower percent expected 6-minute walk distance. On multivariate analysis, only BMI (-0.52 [-0.81-{-0.22}], $p=0.001$) and LatinX ethnicity (-7.40 [-11.55-{-3.25}], $p=0.001$) were significant (Supplemental Table 3).

Discussion

We describe the prevalence of persistent symptoms and impairment in work and activity and cardiopulmonary function in patients 3-4 months after COVID-19 infection.

The majority had mild/moderate COVID-19 with only 22/118 (18.6%) hospitalized during initial illness. Hospitalized patients were older and more likely to be non-white. Hospitalized patients had higher incidence of fever/chills and dyspnea at onset of COVID-19 with the most common symptoms being fatigue, cough, and anosmia, consistent with descriptions of acute COVID-19.² At 3-4 month follow-up, the most common persistent symptoms were fatigue, dyspnea and anosmia, consistent with other reports.⁴⁻⁶ We also noted significant memory problems (17%) and hair loss (12%) at follow-up.

Some of these symptoms are similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), defined by severe and incapacitating fatigue not relieved by rest, post-exertional malaise, unrefreshing sleep, severe cognitive dysfunction, pain, and autonomic dysfunction lasting for > 6 months. Such symptoms have been, in part, attributed to mitochondrial dysfunction and metabolic changes.⁸ Whether “Long COVID” has a similar pathophysiology as ME/CFS remains to be determined.^{8,9} Continued follow-up of these patients will be important to determine final duration of symptoms and further elucidate risk factors and strategies for their mitigation.

Other objective findings in “Long COVID” include myocarditis 2-3 months after diagnosis¹⁰, which may explain the poor performance of this cohort on the 6-minute walk test relative to the expected value based on their gender and age⁷; further cardiopulmonary testing is planned for this cohort.

Two-thirds of patients had at least one symptom at follow-up, half had at least two, and one-third had three or more. On the WPAI, a validated instrument measuring health-related impairments on work productivity and non-work-related activity¹¹, 11.5% of currently employed patients missed work and 38.9% reported impairment at work due to health; half of all patients, including those not currently employed, reported health-related impairment in daily activities. Presence of ongoing long-term symptoms or work impairment did not differ by initial hospitalization status, though hospitalized patients were more likely to have non-work-related activity impairment. Unlike findings in other studies, we did not find an association between sex and presence of persistent symptoms.

It is striking that persistent symptoms and impairment ~4 months after COVID-19 infection were so common, especially since the majority of this cohort did not have complicated COVID-19 and few had risk factors such as underlying heart or lung disease. Much attention has been paid to the acute mortality and morbidity of COVID-19, and it is well recognized that there will be lingering health effects after critical illness.¹² Discussion of mild/moderate COVID-19 cases in the US has mainly been in the context of reducing transmission to others who may be more vulnerable to severe disease and death. However, ours and other recent studies showing high prevalence of ongoing symptoms several months after even mild/moderate initial infection is concerning. Despite significant improvements in case-fatality rates since the beginning of the pandemic, there are no FDA-approved therapies to treat uncomplicated COVID-19. If even a small percent of the 25 million cases in the U.S. have chronic symptoms that affect their work and daily activities, this would be a huge societal burden.

This study has several limitations. Due to logistical issues related to recruitment, hospitalized patients had longer time between COVID-19 diagnosis and follow-up. However, despite this longer time to follow-up, hospitalized patients also achieved lower percent of expected 6-minute walk test distance and were more likely to report health-related activity impairment. Patients were recruited from two separate long-term follow-up studies with slightly different data collection procedures, however 24 patients participated in both studies and results were consistent between both studies for these patients. The small number of patients not recruited from a clinical trial did not have symptoms assessed at the time of COVID-19 onset, therefore recall bias is a concern. Selection bias is possible, as patients electing to participate in follow-up visits after COVID-19 may have more persistent symptoms than the average patient. Generalizability of results is limited given this is a single-institution study; further, patients with more mild or asymptomatic disease may have been less likely to test for COVID-19 and enroll in trials early in the pandemic with limitations in testing availability. We did not collect baseline WPAI and 6-minute walk tests, which would have allowed us to compare assessments over time within individuals.

Conclusion

Persistent symptoms 3-4 months after COVID-19 diagnosis was common with similar levels in hospitalized vs. non-hospitalized patients. Functional impairment at long-term follow-up was higher in hospitalized patients but also prevalent in non-hospitalized patients. With burgeoning cases throughout the country, there is concern for significant morbidity due to persistent symptoms and functional impairment even in patients with uncomplicated COVID-19 and efforts to dissect the cause and mitigate the impact are needed.

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Table 1

| | Total N=118 | Hospitalized N=22 (18.6%) | Non- hospitalized N=96 (81.4%) | P-value |
|--|------------------------|--------------------------------------|---|----------------|
| <i>Male sex (n, %)</i> | 63 (53.4%) | 14 (65.6%) | 49 (51.0%) | 0.29 |
| <i>Age</i> | | | | |
| <i>Mean (SD)</i> | 43.3 (14.4) | 50.6 (15.1) | 41.6 (12.5) | 0.019 |
| <i>Race/Ethnicity</i> | | | | |
| <i>LatinX</i> | 60 (50.8%) | 12 (54.5%) | 48 (50.0%) | 0.004 |
| <i>White</i> | 43 (36.4%) | 3 (13.6%) | 40 (41.7%) | |
| <i>Asian</i> | 12 (10.2%) | 7 (31.8%) | 5 (5.2%) | |
| <i>Native Hawaiian or other Pacific Islander</i> | 1 (0.8%) | 0 (0.0%) | 1 (1.0%) | |
| <i>More than one race</i> | 1 (0.8%) | 0 (0.0%) | 1 (1.0%) | |
| <i>Unknown</i> | 1 (0.8%) | 0 (0.0%) | 1 (1.0%) | |
| <i>Comorbidity present</i> | 39 (33.1%) | 12 (54.5%) | 27 (28.1%) | 0.018 |
| <i>BMI</i> | | | | |
| <i>Mean (SD)</i> | 30.4 (6.3) | 31.6 (6.9) | 30.1 (6.1) | 0.34 |
| <i>Clinical trial participant</i> | | | | |
| <i>Lambda</i> | 67 (56.8%) | 1 (4.5%) | 66 (68.8%) | --- |
| <i>Favipravir</i> | 17 (14.4%) | 0 (0.0%) | 17 (17.7%) | |
| <i>Gilead SIMPLE Trial</i> | 20 (16.9%) | 20 (90.9%) | 0 (0.0%) | |
| <i>Not enrolled in clinical trial</i> | 14 (11.9%) | 1 (4.5%) | 13 (13.5%) | |
| <i>Therapies received</i> | | | | |
| <i>Remdesivir</i> | 21 (17.8%) | 21 (95.5%) | 0 (0.0%) | --- |
| <i>Dexamethasone</i> | 0 (0%) | 0 (0.0%) | 0 (0.0%) | |
| <i>Lambda</i> | 31 (26.3%) | 0 (0.0%) | 31 (32.3%) | |
| <i>Favipravir vs placebo (ongoing study)</i> | 17 (14.4%) | 0 (0.0%) | 17 (17.7%) | |
| <i>No treatment/placebo</i> | 49 (40.8%) | 1 (4.5%) | 48 (50.0%) | |
| <i>Time to follow-up (days)</i> | | | | |
| <i>Mean (SD)</i> | 119.3 (33.0) | 138.6 (21.7) | 114.8 (33.6) | <0.001 |
| <i>Symptoms present at follow-up</i> | | | | |
| <i>Fatigue</i> | 36 (30.8%) | 8 (36.4%) | 28 (29.5%) | 0.53 |
| <i>Dyspnea</i> | 31 (26.5%) | 11 (50.0%) | 20 (21.1%) | 0.006 |
| <i>Loss of taste/smell</i> | 25 (21.4%) | 2 (9.1%) | 23 (24.2%) | 0.12 |
| <i>Myalgias</i> | 21 (17.9%) | 5 (22.7%) | 16 (16.8%) | 0.52 |
| <i>Memory problems</i> | 20 (17.1%) | 5 (22.7%) | 15 (15.8%) | 0.44 |
| <i>Chest pain</i> | 16 (13.7%) | 2 (9.1%) | 14 (14.7%) | 0.49 |
| <i>Hair loss'</i> | 14 (12.0%) | 4 (18.2%) | 10 (10.5%) | 0.32 |
| <i>Cough</i> | 10 (8.5%) | 0 (0.0%) | 1 (1.1%) | 0.63 |
| <i>Headache</i> | 7 (6.0%) | 0 (0.0%) | 7 (7.4%) | 0.19 |
| <i>Congestion/rhinorrhea</i> | 8 (6.8%) | 1 (4.5%) | 7 (7.4%) | 0.64 |
| <i>Nausea/Vomiting/Diarrhea</i> | 8 (6.8%) | 0 (0.0%) | 8 (8.4%) | 0.16 |
| <i>Palpitations</i> | 7 (6.0%) | 0 (0.0%) | 7 (7.4%) | 0.19 |
| <i>Sore throat</i> | 3 (2.6%) | 0 (0.0%) | 3 (3.2%) | 0.40 |
| <i>Fever/Chills</i> | 1 (0.9%) | 0 (0.0%) | 1 (1.1%) | 0.63 |
| <i>Symptom Burden at follow-up</i> | | | | |
| <i>Any Symptom</i> | 79 (66.9%) | 18 (81.8%) | 61 (64.2%) | 0.11 |
| <i>>=2 Symptoms</i> | 59 (50.4%) | 14 (63.6%) | 45 (47.4%) | 0.17 |
| <i>>=3 Symptoms</i> | 38 (32.5%) | 8 (36.4%) | 30 (31.6%) | 0.67 |
| <i>Six minute walk test distance in meters</i> | | | | |
| <i>Mean (SD)</i> | 416.4 (84.8) | 376.0 (72.5) | 426.0 (85.0) | 0.008 |
| <i>Six minute walk test % of expected distance in meters</i> | | | | |
| <i>Mean (SD)</i> | 59.2 (11.7) | 54.4 (8.6) | 60.4 (12.1) | 0.010 |
| <i>Work Productivity/Activity Index (n, N*, %)</i> | | | | |

| | | | | |
|--|----------------|---------------|---------------|------|
| <i>Currently employed</i> | 80/117 (67.3%) | 16/22 (72.7%) | 64/95 (67.4%) | 0.63 |
| <i>Missed work due to health</i> | 9/78 (11.5%) | 2/15 (13.3%) | 7/63 (11.1%) | 0.81 |
| <i>Any Work Impairment due to health</i> | 28/72 (38.9%) | 7/12 (58.3%) | 21/60 (35.0%) | 0.13 |
| <i>Any Activity impairment due to health</i> | 54/106 (50.9%) | 14/19 (73.7%) | 40/87 (46.0%) | 0.03 |

SD=standard deviation, IQR=interquartile range. P value represents Chi-square, Fisher's exact test or independent samples t-test as appropriate. Non-white=Asian (n=12, 10.2%), Native Hawaiian/other Pacific Islander (n=1, 0.8%), American Indian/Alaska Native (n=2, 1.7%). Comorbidities were diabetes (n=20, 16.9%), hypertension (n=13, 11%), asthma/COPD (n=12, 10.2%) and heart disease (n=5, 4.2%). Expected 6 minute walk test distance = $868.8 - [\text{Age} * 2.99] - [\text{Gender} * 74.7]$ where best 6MWD is expressed in meters, age is in years and gender is "women = 1" and "men = 0"; Percent of expected distance = $\text{Distance in meters} \div \text{Expected distance} \times 100$. Any work or activity impairment is defined as any response > 0 on the work and activity impairment scale questions on the WPAI questionnaire.

*Missing data due to incomplete surveys.

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