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Clinical differences in symptomology, characteristics, and risk factors in patients with post-acute sequelae of COVID-19: an experience from a tertiary-care academic center

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus SARS-CoV-2 and has caused significant mortality and morbidity since it was first recognized in Wuhan, China in December 2019. Patients may suffer from a constellation of symptoms termed post-acute sequelae of COVID-19 (PASC). Here we present findings of a retrospective cohort study describing the prevalence and predicting factors of patient-reported post-acute sequelae of COVID-19 (PASC). Categorical variables were summarized as frequency (percentage) and compared between vaccine status groups using Fisher's exact test. Continuous variables were reported as median (range) and compared between the groups using Kruskal-Wallis test. All tests were two-sided with p value <0.05 considered statistically significant. Survey data from 132 patients with a median age of 45 years, 68% female, 83% Caucasian/Non-Hispanic. The most frequently reported PASC symptoms include fatigue (84.8%), dyspnea (54.5%), cognitive dysfunction (53%), myalgias (37.1%), lightheadedness or vertigo (36.4%), chest pain (34.8%), palpitations (34.8%), headaches (34.1%), arthralgias (31.8%), and unrefreshing sleep (31.1%). There is mounting evidence that supports higher prevalence of PASC in women, White/Caucasian, and middle-aged individuals. This knowledge can provide guidance to clinical practices to anticipate and support healthcare and self-care needs for patients at higher risk to developing PASC.

Keywords

Demography, COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has caused significant mortality and morbidity since it was first recognized in Wuhan, China in December 2019. Most patients are asymptomatic or have mild to moderate disease, but 5%–10% of patients develop more severe disease requiring hospitalization for hypoxia, COVID pneumonia, and may require intensive care for non-invasive ventilation or mechanical ventilation. Biochemical evidence demonstrates the replication of SARS-CoV-2 ceases after 4 weeks of acute infection based on viral isolate sampling from the respiratory tract, yet patients may suffer from a constellation of symptoms termed post-acute sequelae of COVID-19 (PASC).[1,2]

Health concerns lasting beyond the first 4 weeks of acute infection can include long COVID or persistent

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WHAT IS KNOWN ABOUT THE SUBJECT?

- Most patients are asymptomatic or have mild to moderate disease.
- 8%–10% develop severe disease requiring hospitalization.
- Long COVID, post-COVID syndrome defines those symptoms not attributable to an alternative diagnosis.

NEW FINDINGS

- 38% of the study population was obese.
- 5% had a significant smoking history.
- 62.9% of the study population was fully vaccinated.
- In our study population, obesity, chronic headache, anxiety, and depression were the predominant comorbidities.

IMPACT ON CLINICAL PRACTICE

- The symptom variability highlights the heterogenous and evolving nature of the condition, and vaccination does not necessarily reduce the risk for PASC, but comorbidities do play a role in the persistence of symptoms, and as clinicians, the focus should be on optimal management of comorbidities, which may reduce persistent complications of COVID-19.

post-COVID syndrome (symptoms lasting weeks to months), multi-organ effects of COVID-19, and the effects of COVID-19 treatment/hospitalization as defined by the Centers for Disease Control.[1] Long COVID, also known as chronic or post-COVID syndrome, is defined by symptoms present beyond 12 weeks, not attributable to an alternative diagnosis and persistent post-COVID syndrome as symptoms occurring up to 12 weeks from the onset of acute infection.[3] Long COVID may manifest as persistent fatigue/tiredness, dyspnea, cough, cognitive dysfunction, and dysautonomia, persistent loss of taste and/or smell, headaches, cough, low-grade fevers, palpitations, dizziness, myalgias, and arthralgias.[1,4]

Survivors of critical illness associated with COVID-19 are at elevated risk of developing post-intensive care syndrome which results in physical, psychiatric, and/or cognitive impairment in 64% of patients 3 months after hospital discharge.[5,6] Multi-organ effects of COVID-19 can include respiratory, cardiovascular, neuropsychiatric, and renal organ systems, and the duration of symptoms is variable.[1]

This study summarizes demographics, symptoms, and risk factors (including vaccination status) for patients seen in the specialty PASC Clinic at tertiary-care academic center with post-COVID-19 symptoms persisting greater than 28 days from acute infection.

Materials and methods

This retrospective study included patients seen in the PASC Clinic at Mayo Clinic Florida with post-COVID-19 symptoms persisting greater than 28 days from acute infection. The patients had been interviewed by a physician and asked to self-report their symptoms to minimize the risk of bias. These reports were reviewed by nurses and subsequently by the physician before they were uploaded to the patient EHR (electronic health record).

The study protocol was approved by the IRB (ID: 20-012275). Patients who were below 18 years of age and did not have either a documented positive COVID test or positive antibody titers were excluded from the study. The data required for the study was extracted from the EHR by a member of the study team. Categorical variables were summarized as frequency (percentage) and compared between those who were unvaccinated (118) vs vaccinated (14) prior to acute infection and groups using Fisher's exact test. Continuous variables were reported as median (range) and compared between the groups using Kruskal-Wallis test. All tests were two-sided with p value <0.05 considered statistically significant. The analysis was done using R4.0.3.

Results

Our sample consisted of a total of 132 patients, with a median age of 45 years. Sixty-eight percent of the sample self-identified as female, while 83% self-identified as being Caucasian/Non-Hispanic. Over 38% of the study population was identified to be obese, while approximately 5% reported a significant smoking history. All baseline characteristics of study participants are summarized in Table 1. The study population demonstrated a wide array of symptoms as part of their PASC experience as summarized in Table 2. In our cohort, the three most common symptoms include fatigue (85%), dyspnea (55%), and cognitive dysfunction (53%). Other common symptoms include myalgia/arthralgia, lightheadedness, chest pain, palpitations, headaches, and unrefreshing sleep.

A summary of the most frequent comorbidities seen in patients with PASC is noted in Table 3. 62.9% of the study population was fully vaccinated at the time of their clinic visit. However, only 14% had been

Table 1. Demographic and baseline risk factors.

Variable	Not vaccinated prior to COVID (N = 118)	Vaccinated prior to COVID (N = 14)	Total (N = 132)	p Value
Age range				0.072
17–29	20 (16.9%)	2 (14.3%)	22 (16.7%)	
30–39	21 (17.8%)	3 (21.4%)	24 (18.2%)	
40–49	38 (32.2%)	2 (14.3%)	40 (30.3%)	
50–59	32 (27.1%)	3 (21.4%)	35 (26.5%)	
60–69	7 (5.9%)	4 (28.6%)	11 (8.3%)	
Gender				0.792
Female	81 (68.6%)	9 (64.3%)	90 (68.2%)	
Male	36 (30.5%)	5 (35.7%)	41 (31.1%)	
Non-binary	1 (0.8%)	0 (0.0%)	1 (0.8%)	
Race				0.804
Missing	1	0	1	
Black	6 (5.1%)	1 (7.1%)	7 (5.3%)	
Caucasian/Non-Hispanic	96 (82.1%)	13 (92.9%)	109 (83.2%)	
Hispanic	10 (8.5%)	0 (0.0%)	10 (7.6%)	
Other	5 (4.3%)	0 (0.0%)	5 (3.8%)	
Education				0.899
Not disclosed	6	1	7	
AA/AS	27 (23.9%)	2 (15.4%)	29 (23.0%)	
Graduate	31 (27.4%)	4 (30.8%)	35 (27.8%)	
High school	19 (16.8%)	3 (23.1%)	22 (17.5%)	
Post-doctorate	2 (1.8%)	0 (0.0%)	2 (1.6%)	
Undergraduate	33 (29.2%)	4 (30.8%)	37 (29.4%)	
Tobacco use				0.497
No	113 (95.8%)	13 (92.9%)	126 (95.5%)	
Yes	5 (4.2%)	1 (7.1%)	6 (4.5%)	
Illicit drugs				1.000
Not disclosed	1	0	1	
No	103 (88.0%)	13 (92.8%)	116 (87.8%)	
Yes	14 (12.0%)	1 (7.1%)	15 (11.3%)	
Alcohol use				0.377
No	74 (62.7%)	11 (78.6%)	85 (64.4%)	
Yes	44 (37.3%)	3 (21.4%)	47 (35.6%)	

Fisher's exact test was used to compare categorical variables between patients vaccinated prior to COVID and patients not vaccinated prior to COVID, Kruskal-Wallis rank sum test used to compare continuous variables between the two groups.

vaccinated prior to their acute COVID infection as illustrated in Supplemental Table 1.

Discussion

The study results summarize the demographics, symptoms, and risk factors/comorbidities for patients seen in the PASC Clinic at Mayo Clinic Florida. This specialty referral-based clinic provides care for patients with ongoing post-COVID-19 symptoms, persisting greater than 28 days from acute infection. Patients coming to the PASC Clinic are from all over the United States and International including South America, Canada, and Mexico. Overall, the demographics of our study population were similar to other published findings, further supporting a higher prevalence of PASC in women, White/Caucasian, and middle-aged individuals.[7–10]

Our findings varied in comparison to other previously published reports. There has been variability in the findings of referral bias among studies because of variability in settings—tertiary-care center vs hospital vs outpatient, variability in the numbers of patients included in the study, as well as variability in study design. A case series of previously hospitalized patients in Italy demonstrated the most common symptoms being fatigue, dyspnea, joint pain, chest pain, and cough.[7,8] A retrospective cohort study performed at Mayo Clinic Minnesota identified pain (90%), fatigue (74%), dyspnea (43%), and orthostatic intolerance (38%) as the most common post-COVID symptoms.[7] Furthermore, a large online survey study identified fatigue (79%), headaches (55%), dyspnea (55%), difficulty concentrating (54%), cough (49%), dysgeusia (45%), diarrhea (44%), and myalgia/arthralgia (44%)

Table 2. PASC symptoms summary.

Variable	Not vaccinated prior to COVID (N = 118)	Vaccinated prior to COVID (N = 14)	Total (N = 132)	p Value
Dyspnea				0.404
0	52 (44.1%)	8 (57.1%)	60 (45.5%)	
1	66 (55.9%)	6 (42.9%)	72 (54.5%)	
Fatigue				1.000
0	18 (15.3%)	2 (14.3%)	20 (15.2%)	
1	100 (84.7%)	12 (85.7%)	112 (84.8%)	
Unrefreshing sleep				0.762
0	82 (69.5%)	9 (64.3%)	91 (68.9%)	
1	36 (30.5%)	5 (35.7%)	41 (31.1%)	
Post-exertional malaise				0.749
0	89 (75.4%)	10 (71.4%)	99 (75.0%)	
1	29 (24.6%)	4 (28.6%)	33 (25.0%)	
Brain fog				0.411
0	57 (48.3%)	5 (35.7%)	62 (47.0%)	
1	61 (51.7%)	9 (64.3%)	70 (53.0%)	
Lightheadedness/vertigo				1.000
0	75 (63.6%)	9 (64.3%)	84 (63.6%)	
1	43 (36.4%)	5 (35.7%)	48 (36.4%)	
Myalgias				0.771
0	75 (63.6%)	8 (57.1%)	83 (62.9%)	
1	43 (36.4%)	6 (42.9%)	49 (37.1%)	
Arthralgias				0.547
0	79 (66.9%)	11 (78.6%)	90 (68.2%)	
1	39 (33.1%)	3 (21.4%)	42 (31.8%)	
Headaches				1.000
0	78 (66.1%)	9 (64.3%)	87 (65.9%)	
1	40 (33.9%)	5 (35.7%)	45 (34.1%)	
Cough				0.644
0	106 (89.8%)	12 (85.7%)	118 (89.4%)	
1	12 (10.2%)	2 (14.3%)	14 (10.6%)	
Chest pain				0.559
0	78 (66.1%)	8 (57.1%)	86 (65.2%)	
1	40 (33.9%)	6 (42.9%)	46 (34.8%)	
Anxiety				0.703
0	99 (83.9%)	11 (78.6%)	110 (83.3%)	
1	19 (16.1%)	3 (21.4%)	22 (16.7%)	
Depression				1.000
0	106 (89.8%)	13 (92.9%)	119 (90.2%)	
1	12 (10.2%)	1 (7.1%)	13 (9.8%)	
Vision problems				1.000
0	95 (80.5%)	12 (85.7%)	107 (81.1%)	
1	23 (19.5%)	2 (14.3%)	25 (18.9%)	
Palpitations				0.770
0	76 (64.4%)	10 (71.4%)	86 (65.2%)	
1	42 (35.6%)	4 (28.6%)	46 (34.8%)	
Heat/cold intolerance				0.359
0	105 (89.0%)	14 (100.0%)	119 (90.2%)	
1	13 (11.0%)	0 (0.0%)	13 (9.8%)	
Anosmia/dysgeusia				1.000
0	102 (86.4%)	13 (92.9%)	115 (87.1%)	
1	16 (13.5%)	1 (7.1%)	17 (12.8%)	
Numbness/tingling				0.359
0	105 (89.0%)	14 (100.0%)	119 (90.2%)	
1	13 (11.0%)	0 (0.0%)	13 (9.8%)	
Nausea/GI symptoms				1.000
0	100 (84.7%)	12 (85.7%)	112 (84.8%)	
1	18 (15.3%)	2 (14.3%)	20 (15.2%)	

p Values result from Fisher's exact test for categorical data with simulated p-value (based on 2000 replicates).
GI, Gastrointestinal.

Table 3. Comorbidities summary.

Variable	Not vaccinated prior to COVID (N = 118)	Vaccinated prior to COVID (N = 14)	Total (N = 132)	p Value
Hypertension				0.105
No	92 (77.9%)	8 (57.1%)	100 (75.7%)	
Yes	26 (22.2%)	6 (42.9%)	32 (24.4%)	
Diabetes				1.000
No	107 (90.7%)	13 (92.9%)	120 (90.9%)	
Yes	11 (9.3%)	1 (7.1%)	12 (9.1%)	
Asthma				0.301
No	93 (78.8%)	13 (92.9%)	106 (80.3%)	
Yes	25 (21.2%)	1 (7.1%)	26 (19.7%)	
Hyperlipidemia				0.058
No	101 (85.6%)	9 (64.3%)	110 (83.3%)	
Yes	17 (14.4%)	5 (35.7%)	22 (16.7%)	
Hypothyroidism				1.000
No	103 (87.3%)	13 (92.9%)	116 (87.9%)	
Yes	15 (12.7%)	1 (7.1%)	16 (12.1%)	
Gerd				0.192
No	90 (76.3%)	8 (57.1%)	98 (74.2%)	
Yes	28 (23.7%)	6 (42.9%)	34 (25.8%)	
Chronic headache				0.064
No	80 (67.8%)	13 (92.9%)	93 (70.5%)	
Yes	38 (32.2%)	1 (7.1%)	39 (29.5%)	
OSA				0.691
No	99 (84.6%)	13 (92.9%)	112 (85.5%)	
Yes	19 (16.1%)	1 (7.1%)	20 (15.1%)	
Obesity				1.000
No	71 (60.1%)	8 (57.1%)	79 (59.8%)	
Yes	47 (39.8%)	6 (42.8%)	53 (40.1%)	
Anxiety				0.083
No	72 (61.0%)	12 (85.7%)	84 (63.6%)	
Yes	46 (39.0%)	2 (14.3%)	48 (36.4%)	
Depression				0.112
No	81 (69.2%)	13 (92.9%)	94 (71.8%)	
Yes	37 (31.3%)	1 (7.1%)	38 (28.7%)	
Insomnia				1.000
No	104 (88.1%)	13 (92.9%)	117 (88.6%)	
Yes	14 (11.9%)	1 (7.1%)	15 (11.4%)	
Allergies				0.425
No	102 (86.4%)	11 (78.6%)	113 (85.6%)	
Yes	16 (13.6%)	3 (21.4%)	19 (14.4%)	
Fibromyalgia				1.000
No	106 (89.8%)	13 (92.9%)	119 (90.2%)	
Yes	12 (10.1%)	1 (7.1%)	13 (9.8%)	

p Values result from Fisher's exact test for categorical data with simulated p-value (based on 2000 replicates).
GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea.

as the most common post-COVID symptoms.[11] The symptom variability seen throughout these studies highlights the heterogeneous and evolving nature of this condition. According to the CDC, this heterogeneity may be due in part to different underlying pathophysiological processes, medical comorbidities, acute disease course, and psychosocial determinates of health.[12]

Our analysis also revealed several medical risk factors/comorbidities commonly seen in patients who developed PASC as summarized in Table 3. The four most common include obesity, anxiety, chronic headaches, and depression. Other common comorbidities experienced in our patients with PASC include gastroesophageal reflux disease, hypertension, chronic arthralgia/myalgia, asthma, hyperlipidemia, obstructive sleep apnea, and allergic rhinitis. These findings are similar to other published reports that demonstrated the presence of many of these same risk factors.[13–15]

Of the 132 patients in our sample, the majority of patients with PASC were unvaccinated at the time of

acute COVID-19 infection (89.4%) as summarized in Supplemental Table 1. Subgroup analysis was performed to identify any significant differences in demographics, symptoms, or risk factors based on vaccination status. Our analysis suggests that in patients with PASC, there were no statistically significant differences in demographics (age, gender, race, education, body mass index, tobacco use, or alcohol use), initial (at the time of acute infection) or current (at the time of PASC Clinic appointment) symptomatology, or risk factors/comorbidities based on vaccination status. Our findings differ from a recent online non-peer reviewed report, which suggested that vaccination was associated with a decrease in PASC symptoms and could serve as a protective factor.[16–19] Furthermore, there were notable differences in the course of acute COVID-19 in the 118 unvaccinated compared to the 14 vaccinated individuals. Patients who were unvaccinated had a more severe acute course (30% developed COVID pneumonia, 30% were hospitalized, and 5% required ICU-level medical care) compared to vaccinated patients (7% developed COVID pneumonia, 14% were hospitalized, and none required ICU-level care). However, there was no significant difference in the comorbidities of patients who were vaccinated vs unvaccinated, and no significant difference in the number of PASC symptoms between the two groups. This appears to suggest that vaccination is not a factor in the number or persistence of symptoms associated with COVID-19; however, the small sample size is a limitation, and we will continue to study this question in larger scale studies from our clinic.

The present study has limitations confined by its observational retrospective design. As a result, additional well-designed prospective studies will need to be performed to further confirm our findings. As our study cohort consisted mostly of participants identified as female and White, there is a need for future studies with a greater degree of ethnic diversity, especially given the increased infection risk in African American and Hispanic communities.[20,21] Furthermore, though all participants were seen in a single specialty clinic in an academic tertiary medical center, this fact could limit our generalizability, as well as introduce selection and referral bias. There are strengths to the present study. First, the study consisted of a moderately-sized study cohort, solely consisting of patients with PASC. Second, all individuals included in the study were assessed in a single specialty clinic, minimizing variability in clinical care and assessment. The healthcare professionals in our PASC Clinic have been engaging in clinical and scholarly efforts in this field since the beginning of the pandemic, adding to their previous findings.[22–25] Third, we provided a concise summary of the demographics, symptoms, and risk factors for patients experiencing PASC and provided an analysis of these factors and clinical outcomes based on vaccination status (Supplemental Table 2).

Conclusion

There is mounting evidence that supports higher prevalence of PASC in women, White/Caucasian, and middle-aged individuals.[7–10] This data can be used to better guide decision-making as clinicians and healthcare managers in response to the rapidly evolving and changing symptomology in patients with PASC. There is also a need for additional research to explore potential etiological factors associated with this risk.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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