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ORIGINAL RESEARCH

Predictors of Postacute Sequelae of COVID-19 Development and Rehabilitation: A Retrospective Study

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Abstract

Objective: To examine the frequency of postacute sequelae of SARS-CoV-2 (PASC) and the factors associated with rehabilitation utilization in a large adult population with PASC.

Design: Retrospective study.

Setting: Midwest hospital health system.

Participants: 19,792 patients with COVID-19 from March 10, 2020, to January 17, 2021.

Intervention: Not applicable.

Main Outcome Measures: Descriptive analyses were conducted across the entire cohort along with an adult subgroup analysis. A logistic regression was performed to assess factors associated with PASC development and rehabilitation utilization.

Results: In an analysis of 19,792 patients, the frequency of PASC was 42.8% in the adult population. Patients with PASC compared with those without had a higher utilization of rehabilitation services (8.6% vs 3.8%, P<.001). Risk factors for rehabilitation utilization in patients with PASC included younger age (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.98-1.00; P=.01). In addition to several comorbidities and demographics factors, risk factors for rehabilitation utilization solely in the inpatient population included male sex (OR, 1.24; 95% CI, 1.02-1.50; P=.03) with patients on angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers 3 months prior to COVID-19 infections having a decreased risk of needing rehabilitation (OR, 0.80; 95% CI, 0.64-0.99; P=.04).

Conclusions: Patients with PASC had higher rehabilitation utilization. We identified several clinical and demographic factors associated with the development of PASC and rehabilitation utilization.

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There is a growing concern that patients infected with SARS-CoV-2 experience persistent symptoms long after the initial symptomatic phase.^{1,2} Currently, there is no established definition to

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describe patients with COVID-19 sequelae; however, a commonly proposed characterization describes illness greater than 4 weeks after acute infection as late sequalae or postacute sequalae of SARS-CoV-2 (PASC).³⁻⁵ The frequency and timeline of PASC is unclear and varies widely with estimations as high as 50%.^{6,7} The presentation also varies with multiple different organ systems affected, and in certain cases, the symptoms are severe enough to cause new disability.⁸⁻¹¹ There is limited information on exacerbating and mitigating factors that would predispose patients to develop PASC.^{6,7} For patients who develop PASC, there is limited information on rehabilitation utilization and efficacy; however, case series have suggested improvement in patient's symptoms with rehabilitation.^{2,12}

Given such a high overall reported frequency of PASC, more information is needed to help triage and recruit at risk patients to rehabilitation programs; thus, we thought to examine patient factors that increase the likelihood of development of PASC. In addition, we examined rehabilitation utilization in patients with PASC and the factors associated with the need for rehabilitation services. By better understanding the resource utilization of patients, we can implement patient-tailored rehabilitation plans to at-risk populations. We hypothesized that patients with more severe disease and more comorbidities would require more rehabilitation services.

Methods

Study design and participants

This study is a retrospective analysis of data from March 10, 2020, to January 17, 2021, of patients with COVID-19 who had their test done at Fairview, a U.S. Midwest health system. Inclusion criteria included all patients with polymerase chain reaction—confirmed COVID-19 treated at a participating hospital. Exclusion criteria included patients who died during their initial acute COVID-19 infection (hospitalized and nonhospitalized patients) and those who opted out of research.

Description of database

The study database was created from Epic electronic health records and included patient demographics (age, sex, race and ethnicity), medications, past medical history, and health encounters from January 1, 2019, to March 17, 2021. Additionally, information regarding state death certificates was obtained from the Minnesota Department of Health.¹³ Patients without prior encounters within each hospital were included in the primary analysis because we did not want to exclude previously healthy patients who developed de novo COVID-19 and subsequent chronic disease.

List of abbreviations:

- ACEI on angiotensin-converting enzyme inhibitor ARB angiotensin receptor blocker
 - CI confidence interval

OR odds ratio

PASC postacute sequelae of SARS-CoV-2

Data definitions

The primary outcome was the development of PASC, which was defined as any patient who had PASC symptoms 31 days or more after COVID-19 and did not have these symptoms at baseline (ie, a patient with chronic obstructive lung disease and a chronic cough that has a cough after COVID-19 would not be considered PASC). This was done to reduce possible confounding factors. Resource utilization related to PASC was categorized using variables (ie, physical medicine and rehabilitation referrals, pulmonary and cardiac rehabilitation) shown in supplemental table S1 (available online only at http://www.archives-pmr.org/). Variables labeled as new denote the patient was not receiving this therapy prior to the diagnosis of COVID-19. A hypothesis-generating analysis was conducted to evaluate the independent association of clinically important variables (exposures) and the need for rehabilitation services. A list of PASC, COVID-19 symptoms, and clinically important variables was catalogued by subject matter experts who lacked direct access to the PASC database but with expertise treating patients with PASC and chronic critical illness.^{14,15} All COVID-19/PASC symptoms listed by the Centers for Disease Control and Prevention as of April 7, 2021, were also included.¹⁶ The overall list of PASC symptoms and clinically important variables hypothesized to be associated with PASC can be found in supplemental table S2 (available online only at http://www. archives-pmr.org/).

Statistical analysis

The University of Minnesota's Natural Language Processing and Information Extraction Laboratory used the list of PASC and COVID-19 symptoms that was developed for this study to extract symptoms from health encounter visits.¹⁷ This process is referred to as the creation of a rule-based gazetteer and relied on linguistic rules constructed from the lexicon to match any mentions of the symptoms and their linguistic variants in notes. Each symptom mention was marked as positive or negative based on whether it occurred in a negated context (eg, "denies cough" would be marked as a negative instance of the cough symptom). The overall performance of the gazetteer was validated against a reference standard set of manually annotated emergency department clinical notes and yielded a precision of 0.90, recall of 0.87, and f1-score of 0.88.¹⁷⁻¹⁹

Statistical analysis was conducted by an independent investigator not involved in variable selection. For descriptive purposes, data were expressed as median and IQR for continuous variables with a skewed observed distribution and as percentages for categorical variables. Student t tests, Mann-Whitney U tests, and Pearson chi-square tests were used in the preliminary analyses as appropriate for the assumed variable distribution. Multivariable logistic regression was performed to evaluate the independent association of variables of interest on the need for rehabilitation services in patients with PASC. Subgroup analyses for rehabilitation utilization were conducted on adults that were hospitalized during their initial COVID-19 infection. An additional adjustment was performed on this population to account for confounding variables (ie, demographics, comorbidities, medications, inpatient data), which can be also found in supplemental table S2 (available online only at http://www.archives-pmr.org/).

All statistical analysis was performed using Stata-MP Version 16.^a Goodness of fit was assessed with Hosmer-

Lemeshow tests, where a *P* value <.1 was considered statistically significant. All other tests were 2-sided, and significance was defined with an α of <0.05.

Results

Outcomes

Overall population

A total of 19,792 patients were included in the analysis (fig 1). In the adult population, the age range was 18 years to 90 years or older. The median age of patients who developed PASC was 51.4 years (range, 32.8-66.4 years), with 38% identifying as male. The characteristics of patients with PASC compared with those without are shown in table 1. The frequency of PASC was 42.8% in the adult population. Table 1 shows the outpatient rehabilitation services that were analyzed, which include physical therapy, occupational therapy, and speech language pathology. Patients with PASC compared with those without PASC had a higher frequency of rehabilitation services during COVID-19 (8.6% vs 3.8%, P<.001) after COVID-19 (8.4% vs 3.0%, P<.001) as well as outpatient physiatry referrals (3.1% vs 1.7%, P<.001) (see table 1).

Factors associated with development of PASC

The factors associated with the development of PASC in all patients can be found in table 2. Male sex was a protective factor against the development of PASC (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.76-0.87; P<.001). Compared with being White, being Asian (OR, 1.26; 95% CI, 1.09-1.45; P=.002), being Black (OR, 1.11; 95% CI, 1.00-1.23; P<.05), living in a rural area (OR, 1.15; 95% CI, 1.07-1.23; P<.001), being non-English speaking (OR, 1.23; 95% CI, 1.10-1.39; P<.01), and being pregnant (OR, 1.18; 95% CI, 1.06-1.30; P<.01) were all risk factors for development of PASC. Patients who required inpatient admission (OR, 1.97; 95% CI, 1.77-2.19; P<.001) and those who required any

rehabilitation program prior to COVID-19 illness were also at higher risk of developing PASC (OR, 1.91; 95% CI, 1.78-2.05; P<.001). Several comorbidities and medications that patients were taking 3 months prior were associated with an increased risk of PASC (see table 2).

Factors associated with rehabilitation utilization in patients with PASC

Risk factors for need for rehabilitation in patients with PASC included younger age (OR, 0.99; 95% CI, 0.98-1.00; P=.01, pregnancy (OR, 3.30; 95% CI, 1.92-5.66; P<.001), and other comorbidities, which can be found in table 3. Risk factors for rehabilitation utilization solely in the inpatient populations were also explored and can be found in supplemental table S3 (available online only at http://www.archives-pmr.org/). Male sex (OR, 1.24; 95% CI, 1.02-1.50; P=.03), older age (OR, 1.01; 95% CI, 1.01-1.02; P<.001), Asian race (OR, 2.48; 95% CI, 1.75-3.50; P<.001), Hispanic race (OR, 2.34; 95% CI, 1.55-3.54; P<.001), and several comorbidities were associated with higher rehabilitation use in the inpatient population. Patients taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) 3 months prior to COVID-19 infections had a decreased risk of needing rehabilitation (OR, 0.80; 95% CI, 0.64-0.99; P=.04) compared with nonusers of ACEIs or ARBs.

Discussion

The purpose of this study was to explore rehabilitation utilization for patients with PASC and identify mitigating and protective factors associated with the development of PASC. In our study, we identified 3 key findings. First, there were high rates of PASC in our patient population. Second, in patients with PASC, younger patients had higher rehabilitation utilization, and several comorbidities were found to be risk factors for rehabilitation utilization, especially in cases of severe COVID-19. Third, patients taking ACEIs and/or ARBs had decreased risk of requiring rehabilitation resource in the inpatient population.

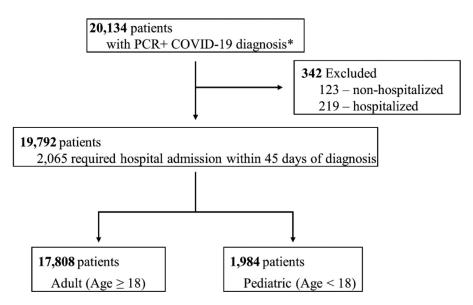


Fig 1 Study diagram of patients included in final analysis of COVID-19 data registry. Abbreviation: PCR, polymerase chain reaction.

Age (J), median (DR) 44.4 (27.9-59.9) 51.4 (32.8-66.4) <.001 Back B052 (72.5) 57.46 (71.8) <.001 Mine B052 (72.5) 57.46 (71.8) <.001 Asian 600 (5.4) 579 (7.2) <.001 Mispanic 463 (A.2) 332 (4.2) Declined 472 (4.2) 218 (2.7) <.001 Must 7475 (65.0) 5768 (69.6) <.001 Body mass indes 29.0 (8.4) 29.9 (8.7) <.001 Body mass indes 10.0 (03.0) 3.0 (1.0-6.0) <.001 Prepension 1317 (11.5) 987 (11.9) .32 Type 2 diabetes 1324 (1.7) 11.71 (1.5) <.001 Type 2 diabetes 1324 (1.4) <.001 <.001 Type 2 diabetes 1324 (1.4) <.001 <.001 Type 2 diabetes 1324 (1.4) 1329 (2.2) <.001 Cornord with educe dejection fraction 226 (2.5) 4.6 (.5, 0.30) <.001 Type 2 diabetes <t< th=""><th>Demographic</th><th>No PASC (n=11,502)</th><th>Yes PASC (n=8290)</th><th>P Value</th></t<>	Demographic	No PASC (n=11,502)	Yes PASC (n=8290)	P Value
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Ventilation 50 (0.4) 113 (1.4) <.001			· ·	
		166 (1 /)	356 (4 3)	< 001
	Intensive care unit			

Demographic	No PASC (n=11,502)	Yes PASC (n=8290)	P Value
Remdesivir	338 (2.9)	653 (7.9)	<.001
Tocilizumab	21 (0.2)	32 (0.4)	.01
Received steroids	138 (1.2)	213 (2.6)	<.001
Bacteremia	45 (6.0)	73 (5.3)	.48
Acute kidney injury	84 (26.0)	162 (26.8)	.80
Venous thromboembolism	79 (0.7)	150 (1.8)	<.001
Rehabilitation			
Rehabilitation during COVID	390 (3.8)	672 (8.6)	<.001
Rehabilitation after COVID	311 (3.0)	658 (8.4)	<.001
Outpatient PMR	199 (1.7)	257 (3.1)	<.001
Dysphagia	15 (0.1)	28 (0.3)	<.01
Pulmonary rehabilitation	3 (0.0)	5 (0.1)	.24
Pulmonary function test	90 (0.8)	196 (2.4)	<.001
Activities of daily living therapy	22 (0.2)	67 (0.8)	<.001
New family therapy	2 (0.0)	9 (0.1)	.01
New cognitive function	3 (0.0)	10 (0.1)	.01
New neuromuscular education	134 (1.2)	210 (2.5)	<.001
New therapy session	262 (2.3)	394 (4.8)	<.001
New aphasia	11 (0.1)	24 (0.3)	<.01

NOTE. Data are presented as n (%) unless otherwise indicated. Terms are according to the International Classification of Diseases. Abbreviation: PMR, physical medicine and rehabilitation.

The frequency of PASC in the adult population was 42.8%. Because of the lack of a standardized definition, the rates reported in other studies often ranges between the low teens to up to more than half of the population. PASC was present in both mild and severe disease; however, having severe disease, defined as requiring hospital admission, was a risk factor for development of PASC. Several comorbidities were risk factors, including hypertension, chronic kidney disease, and asthma, which are similar to risk factors for acute COVID-19 illness.²⁰ There were several medications associated with an increased risk of PASC in the patients who were taking it prior to acute illness; this is likely because of the association of those medications with comorbidities. In our study, non-English speaking populations and being Asian or Black were a risk factor for the development of PASC and being Asian or Hispanic was a risk factor for rehabilitation utilization within the inpatient population. Given this increased risk among certain communities, information regarding PASC needs to be culturally and linguistically accessible as a possible tool to help mitigate this discrepancy.

Resource utilization was high in patients with PASC. Specifically, there was a higher number of therapy sessions and physical medicine and rehabilitation referrals . Patients with PASC underwent more therapy focused on activities of daily living, cognitive function, and neuromuscular education. Younger patients utilized rehabilitation services more overall (in combined severe and nonsevere cases), but for patient's requiring inpatient admission, being older was a risk factor for needing rehabilitation services, and not surprisingly, those who required hospital admission made up the majority of patients needing rehabilitation. In the inpatient population, several demographic factors, including male sex, were risk factors for need for rehabilitation services. In addition, many comorbidities such as hypertension, chronic obstructive lung disease, liver disease, and autoimmune disorders were also

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associated with increased rehabilitation utilization in the inpatient population. These data highlight not only the high rehabilitation utilization of patients with PASC but also speak to the effect PASC can have on society and the workforce. Additionally, this research can provide an introductory framework for hospital systems to implement rehabilitation programs targeting patients with multiple risk factors.

ACEIs and ARBs were associated with decreased risk of needing rehabilitation services in the inpatient population. This supports previous data suggesting possible protective benefits of ACEIs and ARBs on mortality for patients with COVID-19.²¹⁻²³ Possible mechanisms for both medication categories include improved blood pressure control and potential downregulation of the renin-angiotensin-aldosterone system with chronic use leading to decreased inflammation.²⁴⁻²⁶ These data may suggest the benefit is more long-term and may reside across those with more severe disease.²⁷

Study strengths and limitations

This study has many strengths. The large sample size, inclusion of both inpatient and outpatient participants, and extensive but relevant clinical variables allowed for a broader analysis of factors associated with PASC and rehabilitation. Additionally, our definition of PASC as new symptoms not present at baseline as well as the additional adjustments on the inpatient population reduced possible confounders. The study has several limitations. Our results do not suggest a causal inference and could be subject to residual confounding. Only patients diagnosed with COVID-19 at the health care system were included, and thus the population is not indicative of the whole health care system's patient population. There was a lack of a control cohort without COVID-19, making us unable to compare the frequency and symptoms of PASC with a general postviral illness syndrome. The information

Table 2 Multivariate logistic regression of independent factors on the development of PASC				
Demographic	Odds Ratio	CI	P Value	
Male	0.82	0.76-0.87	<.001	
Age	1.00	1.00-1.00	.60	
Race (compared with White)				
Black	1.11	1.00-1.23	<.05	
Asian	1.26	1.09-1.45	.002	
Hispanic	1.09	0.93-1.29	.29	
Declined	0.95	0.79-1.14	.58	
Other	0.96	0.71-1.29	.78	
Rural	1.15	1.07-1.23	<.001	
Non-English speaking	1.23	1.10-1.39	<.01	
Comorbidities				
Pregnancy	1.18	1.06-1.30	<.01	
Body mass index	1.00	1.00-1.00	.48	
Hypertension	1.15	1.06-1.26	<.01	
Asthma	1.14	1.04-1.24	<.01	
Chronic obstructive pulmonary disease	1.13	0.99-1.30	.07	
Interstitial lung disease	1.44	1.11-1.86	<.01	
Heart failure	1.06	0.92-1.23	.40	
Coronary artery disease	1.10	0.97-1.24	.12	
Chronic kidney disease	1.33	1.18-1.50	<.001	
Type 1 diabetes	0.84	0.69-1.03	.10	
Type 2 diabetes	1.09	0.98-1.21	.13	
Cancer	0.97	0.87-1.08	.15	
Liver disease	1.07	0.96-1.20	.22	
Sickle cell	1.39	0.81-2.38	.24	
Anxiety	1.24	1.09-1.41	<.01	
Depression	1.08	0.96-1.22	.10	
Autoimmune	1.29	1.14-1.45	<.001	
Transplant	0.68	0.46-1.00	<.05	
Medications (3mo prior)	0.00	0.40 1.00	<.05	
Aspirin	1.00	0.91-1.11	.97	
Clopidogrel	1.03	0.78-1.35	.85	
Anticoagulation	1.02	0.88-1.18	.85	
Inhaled steroids	1.12	0.99-1.27	.09	
Oral steroids	1.23	1.09-1.39	.09 <.01	
Benzodiazepines	1.12	0.99-1.27	<.01 .08	
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	1.12	0.99-1.27	.08	
Metformin	1.01	0.89-1.19	.68	
Azithromycin	1.16	0.97-1.38	.08	
Tumor necrosis factor inhibitor	1.02			
Cyclosporine/tacrolimus	0.98	0.72-1.46 0.63-1.54	.91 .93	
Testosterone				
Beta blocker	1.26 1.14	0.81-1.96	.32	
	1.14	1.02-1.26	.02	
Antidementia	4.00	4 4 4 9 4	. 004	
Selective serotonin reuptake inhibitor	1.22	1.11-1.34	<.001	
Tricyclic antidepressants	1.36	1.10-1.69	.01	
Serotonin norepinephrine reuptake inhibitor	1.26	1.09-1.45	<.01	
Antipsychotics	1.07	0.00.4.5/	0.0	
Typical	1.24	0.99-1.54	.06	
Atypical	1.11	0.95-1.31	.18	
Both	1.47	0.96-2.23	.07	
Other				
Inpatient	1.97	1.77-2.19	<.001	
Rehabilitation before COVID	1.91	1.78-2.05	<.001	

was also extracted from the electronic medical record from 1 hospital system and taken from problem lists and notes, making data collection not standardized and possibly clinician-dependent. Medications listed for patients do not ascertain actual medication use. Patients could have also received care at different health care systems, and that information would not have been included. Additionally, there was no objective data collection analyzed (ie, pulmonary function tests or computerized tomography imaging).

Table 3 Multivariate logistic regression of independent factors on rehabilitation ut			
Demographic	Odds Ratio	CI	P Value
Male	0.84	0.65-1.08	.18
Age	0.99	0.98-1.00	.01
Race			
Black	0.92	0.60-1.42	.71
Asian	1.03	0.63-1.68	.91
Hispanic	1.36	0.72-2.59	.34
Declined	2.22	0.77-6.38	.14
Other	1.00	0.34-2.95	>.99
Rural	0.99	0.74-1.32	.93
Non-English speaking	1.12	0.73-1.72	.59
Comorbidities			
Pregnancy	3.30	1.92-5.66	<.001
Body mass index	1.00	0.99-1.02	.58
Hypertension	1.20	0.84-1.72	.31
Asthma	1.37	1.00-1.85	<.05
Chronic obstructive pulmonary disease	1.13	0.82-1.56	.46
Interstitial lung disease	1.69	1.02-2.78	.04
Heart failure	1.29	0.94-1.78	.12
Coronary heart disease	1.20	0.87-1.64	.26
Chronic kidney disease	1.09	0.79-1.49	.61
Type 1 diabetes	1.42	0.84-2.39	.19
Type 2 diabetes	0.76	0.55-1.04	.09
Cancer	0.85	0.62-1.15	.29
Liver disease	1.17	0.85-1.59	.34
Sickle cell	1.23	0.10-14.53	.87
Anxiety	1.17	0.73-1.89	.51
Depression	0.93	0.60-1.46	.76
Autoimmune	0.92	0.63-1.32	.64
Transplant	0.88	0.31-2.48	.80
Medications (3mo prior)			
Aspirin	1.09	0.81-1.45	.58
Clopidogrel	0.76	0.40-1.44	.40
Anticoagulation	0.93	0.65-1.32	.68
Inhaled steroids	0.73	0.50-1.06	.10
Oral steroids	1.24	0.86-1.77	.25
Benzodiazepines	1.50	0.93-2.41	.10
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	1.16	0.86-1.56	.32
Metformin	0.75	0.50-1.13	.17
Azithromycin	1.07	0.62-1.85	.82
Tumor necrosis factor inhibitor	2.98	0.49-18.10	.24
Cyclosporine/tacrolimus	1.12	0.33-3.79	.86
Beta blocker	1.36	1.00-1.85	.05
Selective serotonin reuptake inhibitor	0.90	0.64-1.26	.54
Tricyclic antidepressants	2.01	0.99-4.09	.05
Serotonin norepinephrine reuptake inhibitor	1.02	0.64-1.61	.95
Antipsychotics	1.00	0 70 0 67	20
Typical	1.39	0.72-2.67	.32
Atypical	0.90	0.55-1.45	.65
Both	0.56	0.21-1.50	.25
Other Dehabilitation before COVID	0.05	0 72 4 05	70
Rehabilitation before COVID	0.95	0.73-1.25	.73

Finally, the overall missingness of data were relatively low; only 3 variables had any missingness >0.2%: 17.8% of patients were missing body mass index, 4% were missing comorbidity data, and 6% of patients were missing race and ethnicity data. Given the low rate of missingness, multiple imputation was not done, and a complete case analysis was conducted for multivariable analysis.²⁸

Conclusions

Our study demonstrated a high frequency of PASC. Patients with PASC had a high amount of resource utilization, and there were several demographic features and comorbidities that were associated with greater rehabilitation utilization. This study highlights the need for continued development of interdisciplinary teams and care facilities to address the needs of patients post COVID-19 and provides a starting point for hospital systems to help triage at-risk patients. Additional studies are needed that include a control group without COVID-19 to accurately assess incidence, symptom presentations, and factors specific to PASC and patient rehabilitation needs compared with general viral illnesses.

Supplier

a. Stata-MP Version 16; StataCorp, College Station, TX.

Keywords

COVID-19; Rehabilitation; Function

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