SARS-COV-2 re-infection and incidence of post-acute sequelae of COVID-19 (PASC) among essential workers in New York: a retrospective cohort study

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The Lancet Regional Health - Americas 2025;42: 100984

Published Online 8 January 2025
https://doi.org/10.1016/j.lana.2024.100984

Summary

Background After surviving Coronavirus Disease 2019 (COVID-19), some people develop symptoms known as post-acute sequelae of COVID-19 (PASC). PASC is an emerging phenomenon yet to be fully understood, and identifying risk factors has been challenging. This study investigated the association between the number of COVID-19 episodes and the incidence of PASC among essential workers.

Methods We analyzed data from 2511 essential workers, mainly first responders, with confirmed polymerase chain reaction, antibody, or antigen-positive test results for SARS-CoV-2 infection from March 2020 to February 2024. Data were collected through in-person questionnaires and surveys sent via text and email, internal medical records, follow-up calls, and external medical records. Participants who reported continuation or the development of new symptoms three months after the initial SARS-CoV-2 infection, with symptoms lasting for at least two months, were categorized as having PASC, while those without any COVID-19 or whose symptoms resolved were classified as non-PASC. PASC was common in this cohort so we used a Poisson regression model to compute multivariable-adjusted Relative Risk (RR) for the association between risk of PASC and SARS-CoV-2 re-infection, severity, and vaccination status at first infection.

Findings A total of 475 (prevalence = 18.9%, [95% confidence interval] = [17.4–20.5]) PASC patients were identified. The mean (standard deviation (SD)) age of participants who experienced PASC (54.8 (7.2) years) was similar to those who did not (54.2 (7.4) years). There were 403 (16.1% [14.6–17.5]) participants who experienced multiple instances of COVID-19. After adjusting for relevant demographic, lifestyle, and clinical variables, we found a significant association between the risk of experiencing PASC and multiple SARS-COV-2 infections (RR = 1.41 [1.14–1.74]), severe COVID-19 (RR = 3.17 [2.41–4.16]), and being unvaccinated at first infection (RR = 3.29 [2.46–4.41]).

Interpretation Although the pathogenetic mechanism for PASC remains unclear, identifying risk factors such as lack of vaccination or re-infection can assist in better understanding and managing the condition.

Funding National Institute on Aging (NIH/NIA R01 AG049953) and Centers for Disease Control and Prevention (CDC/NIOSH U01 OH011864) and (CDC/NIOSH U01 OH012275).

Keywords: COVID-19; Post-COVID-19; SARS-COV-2; Reinfection; Severity; Vaccination

Introduction

A growing concern about the potential intermediate and long-term adverse effects of COVID-19 on multiple body organs and systems continues to emerge.[1–3] Most individuals who contract SARS-CoV-2 virus recover within three weeks. However, some individuals develop

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Research in context

Evidence before this study

We searched Pubmed, Scopus and Google Scholar for original articles that studied the risk factors of post-acute sequelae of Coronavirus disease (PASC) or Long COVID from the Coronavirus disease (COVID-19) pandemic declaration date by WHO (March 11, 2020) to December 31, 2023. Our key search terms were "predictors", "risk factors", "determinants" AND "post-acute sequelae of SARS-CoV-2 ", "post-acute sequelae of COVID-19, "Post-COVID", or "Long COVID". Potential risk factors reported by some of the studies include demographic characteristics such as older age, female sex, white (non-Hispanic) and Hispanic. Other studies identified anthropometric and lifestyle factors such as high body mass index and smoking; clinical factors like diabetes; and socioeconomic risk factors including lower income and inability to adequately rest weeks following SARS-CoV-2 infection as likely risk factors. We also found evidence linking the risk of PASC to COVID-19 severity as well as vaccination, but a gap remains in the understanding of the impact of multiple COVID-19 episodes and incidence of PASC.

Added value of this study

This study seeks to understand the prevalence and risk factors of PASC among a unique population of essential workers, mainly first responders. To the best of our knowledge, this is the first study to assess the association between SARS-CoV-2 reinfection and the incidence of PASC, especially among essential workers who were highly at risk of developing COVID-19 because of the nature of their jobs. The prevalence of PASC reported in this study supports those previously reported in other populations. We found that SARS-CoV-2 reinfection increases the likelihood of developing PASC by 1.24-fold. Repeated infections (along with a possible decrease in viral load clearance) can cause an increase in the presence of the SARS-CoV-2 genome in the body and thus may lead to the development of PASC.

Implications of all the available evidence

As we continue to understand the medium and long-term impact of acute COVID-19 and the pathogenetic mechanism of PASC, identifying associated risk factors can assist in better understanding and managing the health condition. Linking these factors to other identified potential pathologies, especially with similar clinical pictures and etiological causes, could better help understand the pathology as well as manage the health impact of PASC.

conditions or symptoms that may commence after the initial recovery from acute COVID-19 or persist for months or years after the initial illness. Post-acute sequelae of COVID-19 (PASC), or "Long COVID," are a wide range of health problems, signs, symptoms, and conditions that develop following an acute COVID-19 episode.[4,5] As the World Health Organization (WHO) described, these post-acute COVID-19 conditions occur in some individuals with a history of asymptomatic to severe COVID-19 within three months after their infection and persist for at least eight weeks.[5] Over a hundred PASC symptoms have been reported, including chest pain, cognitive dysfunction, shortness of breath or difficulty breathing, brain fog, headache, fatigue, and others generally impacting multiple organs and daily functioning.[3,4,6,7]

PASC is an emerging phenomenon yet to be fully understood; thus, estimating its prevalence and identifying risk factors has been challenging. Studies have revealed that about 10–20% of people who had COVID-19 could develop post-COVID conditions that might be diagnosed as PASC.[3,8–10] A conservative estimate revealed that at least 65 million people globally experienced PASC, with cases increasing daily.[3] In 2022, about 7.0% of US adults with a history of SARS-COV-2 infection reported ever had PASC,[11] and the Canadian COVID-19 Antibody and Health Survey revealed that 17.2% of Canadian adults with a history of SARS-CoV-2 infection experienced longer-term symptoms.[10] An estimated 1.9 million UK adults (2.9% of the population) self reported experiencing PASC three years after the pandemic.[12]

PASC is likely caused by several overlapping potential factors. A study of 78,252 patients diagnosed using the ICD-10 code U09.9 for post-COVID conditions reported that 33% have no identified pre-existing conditions.[13] Potential risk factors include demographic characteristics such as older age,[14] female sex[11,14,15] and Whites (non-Hispanic) and Hispanics[11]; anthropometric and lifestyle factors such as high body mass index and smoking[16]; clinical factors like diabetes[16]; and socioeconomic risk factors including lower income and inability to adequately rest following SARS-CoV-2 infection.[17,18] There is an increasing need for more research to address many questions around PASC, especially how it presents among vaccinated and non-vaccinated populations and how it is influenced by COVID-19 severity and reinfections. Although the risk of developing PASC exists in both symptomatic and asymptomatic SARS-CoV-2 infection,[16] a recent study found the condition prevalent among critically infected and unvaccinated patients.[19] More studies are required to improve the current knowledge deficit on the relationship between PASC and SARS-CoV-2 infection severity, vaccination status, and reinfection. Thus, this study aims to investigate the association between SARS-CoV-2 re-infection and the incidence of PASC among essential workers enrolled at Stony Brook University World Trade Center

(WTC) Health and Wellness Monitoring Program. We hypothesized that individuals with two or more SARS-CoV-2 infections are at higher risk of experiencing PASC.

Methods

Study population and data sources

This is a retrospective cohort study of essential workers (mainly first responders such as firefighters and other emergency workers/volunteers who provided support and care to victims of World Trade Center Disaster) enrolled in the Stony Brook University World Trade Center Health and Wellness Monitoring Program with antigen, antibody or polymerase chain reaction (PCR) antigen or antibody tests for SARS-CoV-2 infection confirmed from March 2020 to most recent medical visit (as late as February 29, 2024). As described in our previous publication,[20] Stony Brook University operates two clinics in Long Island New York (Westbury and Commack) that provide annual monitoring visits to essential workers (the majority of whom are in active service now or were during the pandemic, and a small number who have retired or are on medical leave). Since the COVID-19 pandemic, the program has included monitoring COVID-19 symptoms, testing, and status. Data was collected over time through in-person questionnaires and surveys sent via text and email, internal medical records, follow-up calls, and external medical records obtained with the release of health information forms.[20]

Outcome

There is currently no diagnostic test for PASC, so we followed the WHO guidelines in identifying participants who experienced PASC. Participants within the COVID-19 cohort who experienced the continuation or development of at least one new symptom that emerged within three months after the initial SARS-CoV-2 infection and persisted for at least two months without other concurrent explanation were assigned to the PASC group. In contrast, those without such experience were placed in the non-PASC group. The PASC symptoms were classified as shown in Table 1. These persistent or reoccurring symptoms range from ≥4 weeks with unspecified duration to more than three years from the onset of COVID-19.

Study variables

We linked COVID-19-related information to demographic, lifestyle, and anthropometric data in the clinical database. Self-reported COVID-19-related information, mainly frequency of SARSCOV-2 infections [average and modal number of infections among the participants was one while the maximum number of infections was four], infection severity [classified by clinicians into asymptomatic/mild, moderate and severe based on NIH COVID-19 clinical spectrum guidelines[20]], and vaccination status on first SARS-COV-2 infection, were included in the study. We adjusted for demographic variables, including age, gender, race/ethnicity (White, Black, Hispanic, and others/multiracial) and highest educational level (<high school, high school, some college and university degree); smoking status; body mass index (Kg/m^2); and other clinical information, including history of diabetes and hypertension.

Neurological	Respiratory	Gastrointestinal	Others
I. Central nervous system - Loss/Altered Taste/Smell - Mental Fog - Phantom Smells - Metallic taste - Dizziness/lethargy - Loss of balance - Vertigo - Tinnitus - Headache/Migraine II. Peripheral nervous system - Numbness and tingling in arms or legs - Nerve pain in extremities III. Psych - Anxiety - Depression	- Dyspnea - Sore throat - Congestion - Runny nose - Wheezing - Cough - Chest pain - Chest tightness - Home Oxygen - Asthma - Sinus pressure/ pain	- Nausea - Vomiting - Diarrhea - Weight loss - GERD/ Heartburn	I. Musculoskeletal - Body aches - Back pain - Myalgias II. Cardiac - Palpitations - Fluttering - Rapid heart rate III. Fatigue - Fatigue - Very Tired - Low energy - Malaise VI. Unspecific - Fever and rashes

Note: GERD, Gastroesophageal reflux disease.

Table 1: **Classification of PASC symptoms among the participants.**

Statistical analysis

The prospective cohort currently includes 2513 COVID-19 sub-cohort participants, and we analyzed data from 2511 participants who consented to participate in the study. We tested normality and homogeneity of variances through Levene's and Bartlett's tests, respectively. We used Wald's approach to compute the 95% confidence intervals around prevalence values of post-acute sequelae of COVID-19 within our sample population. Bivariate analyses were used to compare each categorical variable (Chi-square) and continuous variable (Student's t-test) with the incidence of PASC. We further conducted multivariable–adjusted analyses to generate models that adjusted for all covariates. However, since log-odds are over-estimated when outcomes are common, as is the case for PASC in this study, we used Poisson regression to compute the relative risk (RR) for the association between incidence of PASC and SARS-COV-2 re-infection (frequency), severity and vaccination status at first SARS-CoV-2 infection.[21] We plotted the log of the predicted values for the regression model against an independent variable to assess linearity assumption for the Poisson regression model. Variables associated with the incidence of PASC in the initial bivariate analyses, including age, hypertension, SARS-CoV-2 re-infection, infection severity, and vaccination status at first infection, were combined in regression model 1. Subsequently, we computed all-inclusive

	PASC (n = 475)	Non-PASC (n = 2036)	Total (n = 2511)	P-value
	Mean (SD)	Mean (SD)		
Age in years	54.8 (7.2)	54.2 (7.4)	54.3 (7.4)	0.096
Body mass index (kg/m^2)	31.6 (5.3)	31.2 (5.4)	31.3 (5.34)	0.15
	n (%)	n (%)	n (%)	
Gender; Female	47 (9.9)	159 (7.8)	206 (8.2)	0.14
Race/Ethnicity				
White	313 (65.9)	1377 (67.6)	1690 (67.3)	0.50
Black	20 (4.2)	66 (3.3)	86 (3.4)	
Hispanic	27 (5.7)	92 (4.5)	119 (4.7)	
Others	115 (24.2)	501 (24.6)	616 (24.5)	
Highest educational level				
<High school	22 (4.6)	67 (3.3)	89 (3.5)	0.30
High school	60 (12.6)	316 (15.5)	376 (15.0)	
Some college	210 (44.3)	921 (45.2)	1131 (45.1)	
University degree	134 (28.2)	534 (26.3)	668 (26.6)	
Unknown	49 (10.3)	198 (9.7)	247 (9.8)	
Occupation				
Law enforcement	202 (42.5)	948 (46.6)	1150 (45.8)	0.112
Others (e.g. firefighters, healthcare, construction workers etc.)	273 (57.5)	1088 (53.4)	1361 (54.2)	
Smoking status				
Never smoker	302 (63.6)	1258 (61.8)	1560 (62.1)	0.44
Former smoker	129 (27.2)	548 (26.9)	677 (27.0)	
Current smoker	44 (9.2)	230 (11.3)	274 (10.9)	
Diabetes	64 (13.5)	222 (10.9)	286 (11.4)	0.11
Hypertension	180 (37.9)	648 (31.8)	828 (33.0)	0.011

Note: PASC, Post-acute sequelae of COVID-19; P-values reported from Welch's t-test using the assumption of unequal variance for "Age" and "Body Mass Index" while others through chi-square (χ^2) tests.

Table 2: **Demographic and clinical information categorized by post-acute sequelae of COVID-19.**

adjusted RRs [95% C.I.] for the risk of PASC in model 2 based on all potential covariates previously identified in the study variables section. Statistical analyses were conducted using Stata 17/MP [StataCorp].

Consent and ethical consideration

General written informed consent was obtained from all participants, and no incentive was provided to participate in the study. This study followed the "Strengthening the Reporting of Observation Studies in Epidemiology (STROBE)" reporting guideline. The Stony Brook University Ethics Review Board approved this study (#2021-00397).

Power analysis

The sample was recruited prior to the COVID-19 pandemic and COVID-19 infections and PASC symptoms were identified naturalistically, so sample size was not controlled by the researcher. A *post-hoc* power analysis revealed that with the current sample, our analytic protocol had 80% power to detect an increase in the prevalence of PASC from 19.0 to 25.4% or an increase of 6.3 percentage points (consistent with RR >1.33).

Role of the funding source

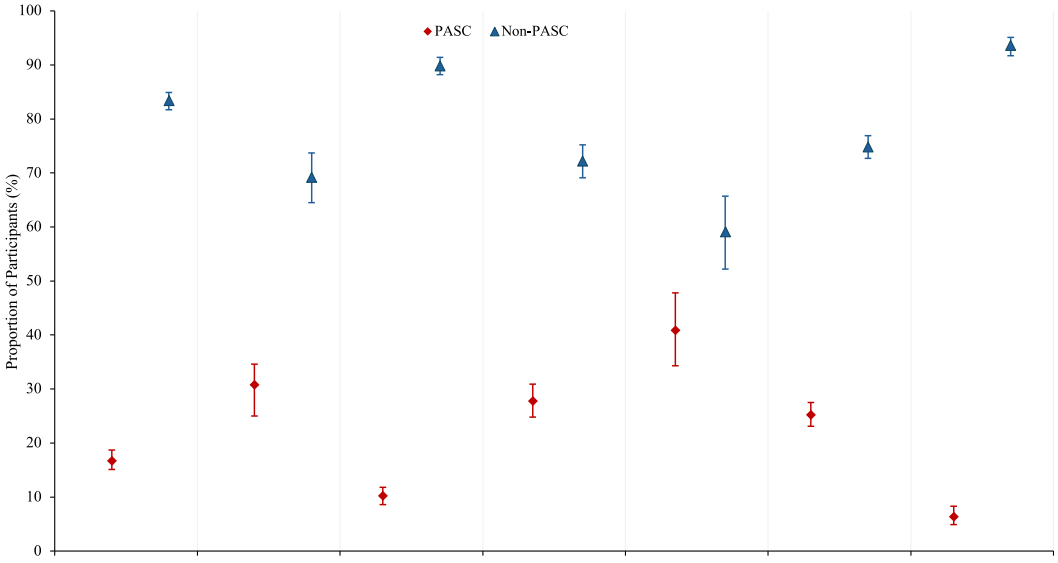
The funders of this study had no role in study design, data collection, analysis, interpretation, and manuscript writing.

Results

We identified 475 (18.9%; 95% CI = [17.4–20.5]) cases of PASC and 403 (16.1%; 95% CI = [14.6–17.5]) participants with multiple SARS-COV-2 infections out of the 2511 COVID-19 cohort essential workers. Participants in both PASC and non-PASC groups had similar demographic and clinical information (Table 2). The bivariable analysis to determine the association between each demographic and clinical variable shows that having a history of hypertension (P = 0.011) was significantly associated with the risk of PASC (Table 2). The mean (SD) age of 54.8 (7.2) years for participants who experienced PASC was higher than the non-PASC group with 54.2 (7.4) years. A higher proportion (37.9%) of the PASC group had a history of hypertension compared to 31.8% of the non-PASC group (Table 2).

We also found that SARS-CoV-2 re-infection (P < 0.001), infection severity (P < 0.001) and vaccination status at first infection (P < 0.001) were significantly associated with incidence of PASC. A higher proportion (30.8%; [25.0–34.6]) of participants who had multiple SARS-COV-2 infections experienced PASC compared to those with single SARS-CoV-2 infection (16.7%; [15.1–18.7]). As shown in Fig. 1, higher proportions of participants with severe (40.9%; [34.3–47.8]) and moderate (27.8%; [24.8–30.9]) SARS-CoV-2 infection experienced PASC as compared to mild/asymptomatic COVID-19 patients (10.2%; [8.6–11.8]). Similarly, a large proportion (25.2%; [23.1–27.5]) of unvaccinated participants at first SARS-CoV-2 infection experienced PASC (Fig. 1).

In the multivariable regression model that accounts for all covariates (Model 2; Table 3), we found a significant increase (RR = 1.41, [1.14–1.74]) in the risk of PASC among those who had multiple SARS-CoV-2 infections. Similarly, participants who experienced moderate (RR = 2.33, [1.88–2.87]) and severe (RR = 3.17, [2.41–4.16]) first SARS-COV-2 infection were at higher risk of developing PASC when compared to those who were mild/asymptomatic. Those who were unvaccinated when they were first infected were at greater risk of PASC (RR = 3.29, [2.46–4.41]) compared to those vaccinated. However, hypertension, significantly associated with the incidence of PASC in the bivariate analysis, was not significant in the multivariable regression model (Table 3).



	Infection Frequency				Infection Severity						Vaccination status at 1st Infection			
	Prop. (%)	95% CI	Prop. (%)	95% CI	Prop. (%)	95% CI	Prop. (%)	95% CI	Prop. (%)	95% CI	Prop. (%)	95% CI	Prop. (%)	95% CI
PASC	16.7	15.1, 18.7	30.8	25.0, 34.6	10.2	8.6, 11.8	27.8	24.8, 30.9	40.9	34.3, 47.8	25.2	23.1, 27.5	6.4	4.9, 8.3
Non-PASC	83.4	81.7, 84.9	69.2	64.5, 73.7	89.8	88.2, 91.4	72.2	69.1, 75.2	59.1	52.2, 65.7	74.8	72.7, 76.9	93.6	91.7, 95.1

Fig. 1: Risk of post-acute sequelae of COVID-19 (PASC) by COVID-19 severity and vaccination status. Note: Prop., Proportion; CI, Confidence Interval; PASC, Post-Acute Sequelae of COVID-19.

Discussion

This study seeks to identify possible risk factors that could be linked to PASC. While some possible microscopic causes and macroscopic pathogenetic mechanisms of PASC continue to be studied, the full spectrum of its risk factors remains unknown. To the best of our knowledge, this is one of the first original research studies to examine the association between the SARS-CoV-2 re-infection and the incidence of PASC. We found 18.9% overall prevalence of PASC, which aligns with the prevalence reported in previous studies.[22–27] We found a significant association between the risk of PASC and multiple SARS-CoV-2 infections, severity of acute COVID-19, and being unvaccinated at first infection. However, we do not find a significant association between the incidence of PASC and demographic factors (mainly age, gender, race/ethnicity and educational level), smoking status and other clinical information (mainly body mass index, hypertension and diabetes status). Although previous studies have reported varied likelihoods of developing PASC based on various demographic groupings,[22,28,29] our study participants are mostly Caucasian men at midlife with similar levels of education and occupations.

Our study indicates that multiple SARS-CoV-2 infections may increase the risk for PASC even after accounting for other major, established, risk factors for PASC including acute COVID-19 severity and COVID-

	Model 1			Model 2[a]		
	RR	95% CI	P-value	RR	95% CI	P-value
Age (*years*)	1.01	(0.99, 1.02)	0.44	1.00	(0.99, 1.02)	0.55
Hypertension; *Yes*	1.19	(0.99, 1.44)	0.068	1.21	(0.99, 1.48)	0.057
Multiple SARS-CoV-2 Infections	1.40	(1.14, 1.72)	0.0010	1.41	(1.14–1.74)	0.001
COVID-19 Severity (ref: *Mild/Asymptomatic*)						
Moderate	2.36	(1.92, 2.90)	<0.0001	2.33	(1.88, 2.87)	<0.0001
Severe	3.22	(2.46, 4.20)	<0.0001	3.17	(2.41, 4.16)	<0.0001
Unvaccinated at first SARS-COV-2 infection	3.21	(2.41, 4.28)	<0.0001	3.29	(2.46, 4.41)	<0.0001

[a]Model adjusted for gender, race, highest educational level, body mass index, smoking status, and diabetes history. RR, Relative Risk; CI, Confidence Interval.

Table 3: **Multivariable Poisson regression models for predictors post-acute sequelae of COVID-19.**

19 vaccination history. This finding aligns with report from review studies on the risk and symptoms of long COVID, and infection with variants of SARS-CoV-2.[30,31] Similarly, findings from a recent study conducted in Mexico reported that PASC was significantly more prevalent among patients who had reinfection.[22] Multiple SARS-CoV-2 infections can increase the severity of the clinical picture,[32] both in terms of mortality from all causes and as a risk of COVID-19-related hospitalization during the acute phase of reinfection.[32] Repeated infections (along with a possible decrease in viral load clearance) can cause an increase in the presence of the SARS-CoV-2 genome in the body and thus may lead to the development of PASC.[33] This mechanism appears similar to causal factors in myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS).[3,34] In addition to this possible causal factor, PASC and ME/CFS also share some symptoms that affect the functional status of patients.

The severity of the acute COVID-19 episode appears to be linked to the likelihood of developing PASC in the subsequent period.[35] A significant proportion of participants with severe SARS-CoV-2 infections experienced PASC. Experiencing persistent physical symptoms, post-COVID-19 was linked with severe acute illness of SARS-CoV-2 infection in a multinational Nordic study.[36] Organ damage often presents simultaneously in multiple systems due to acute COVID-19 infection, plausibly increasing the risk of long-term symptoms due to the infection and the development of a completely new syndrome.[37] This effect is consistent with post-intensive care syndrome, where long-term effects are present in people admitted to intensive care units due to the severity of their clinical picture caused by other infectious and non-infectious diseases.[38] However, the severity of the clinical presentation does not seem to be the only factor that plays a role in the pathogenesis of PASC, as even asymptomatic patients can develop long-term symptoms, albeit to a lesser extent.[39]

One last finding from our study worth emphasizing is the role of vaccination in the risk of developing PASC. Among those who later developed PASC, we found that the risk of PASC was much higher among individuals who were unvaccinated at the time of their first SARS-CoV-2 infection. In this study, most of those individuals were infected prior to the advent of vaccination and, therefore, had little choice in how best to prevent COVID-19 infections. However, it is important to note the role of vaccines in preventing PASC, especially in cases where a person has already been infected with COVID-19 or has even developed PASC. In general, the safest way to avoid contracting PASC is to prevent SARS-CoV-2 infection. Vaccination against COVID-19 has been proven effective in infection control, as well as other measures such as social distancing, proper use of personal protective equipment, or personal hygiene practices. Our study findings are consistent with some findings in the literature, which indicate that the incidence of PASC among COVID-19-vaccinated individuals would be lower than among unvaccinated individuals.[19,25,40–43] Although vaccination has not been established to rescind viral persistence, it reduces symptom severity and improves well-being in post-COVID-19 or PASC.[42]

Strengths and limitations

This is one of the first original studies examining the association between multiple COVID-19 episodes and incidence of PASC. The study used a relatively large sample size, giving power to the study findings. In addition, we adjusted for the most recognized potential risk factors for PASC to lessen confounding effect. However, the study has some limitations worth mentioning. Most study measurements, such as PASC symptoms, were self-reported and thus may be subject to recall bias. Rapid antigen test used during the peak of the pandemic might not accurately detect low viral loads or asymptomatic cases of SARS-CoV-2 infection. Also, the study design might be affected by unmeasured confounding and residual confounding due to measurement error in confounders. The study cohort was mostly Caucasian men in their mid-age with relatively similar levels of education; thus, generalizability of results is limited.

Conclusion

Our study revealed that the risk of PASC was significantly higher among individuals with multiple COVID-19 episodes, severe COVID-19 and unvaccinated at first infection. Although researchers have not yet provided a clear answer to the pathogenetic mechanism of PASC, identifying risk factors can assist in better understanding and managing the health condition. Linking these factors to other identified potential pathologies, especially with similar clinical pictures and etiological causes, could better help understand the pathology and health impact.

Contributors

TKB, SAPC, OM and BJL, conceptualized the original idea and designed the study. TKB and SAPC developed the analysis plan. MC, ZS, DC, BRV, AF and OAM acquired the data. ZS and MC verified the primary dataset. Analysis was done by TKB and reviewed by SAPC and JM. TKB and SN wrote the first draft of the manuscript and was revised by JM, SAPC, and JK. All authors contributed to interpreting the results and critically revising the final draft, had full access to all data in the study and accept full responsibility for publication submission.

Data sharing statement

This work uses sensitive health data and other information of patients enrolled in the Stony Brook University World Trade Center (SBU-WTC) Health and Wellness Monitoring Program. All data and related documentation underlying the reported findings will be made available after anonymization of potentially identifying information. Data will be made

available after publication of this article and up to three years afterwards. Authors will share the data with qualified investigators whose proposal of data use has been approved by an internal review committee.

Declaration of interests

We declare no competing interests.

Acknowledgements

We would like to acknowledge ongoing funding support by the National Institute on Aging (NIH/NIA R01 AG049953) and the National Institute for Occupational Safety and Health (CDC/NIOSH U01 OH011864).

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