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Prevalence and Risk Factors of Post-Acute Sequelae of COVID-19 Among United States Veterans

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Abstract

Prevalence and Risk Factors of Post-Acute Sequelae of COVID-19 Among United States Veterans

By Michela Stephens

Introduction: There is evidence for persisting symptoms and incident conditions after an acute infection with SARS-CoV-2. Early identification of the prevalence and key risk factors for post-acute sequelae of COVID-19 (PASC) is a public health priority. To better understand PASC in the Veteran population, this study aims to determine the prevalence of PASC and identify risk factors associated with its development. This study also aims to determine if post-acute sequalae of COVID-19 risk varies by time period of infection.

Methods: This retrospective cohort study included 363,825 active Veterans that tested positive for COVID-19 between February 1, 2020, and September 30, 2022. risk factors of interest included sociodemographic, social determinants of health (SDOH), and clinical characteristics, The primary outcome was the development of PASC 90 to 180 days following an acute infection with SARS-CoV-2. Multivariate logistic regression was utilized to examine factors associated with post-acute sequelae of COVID-19.

Results: Of the 363,825 Veterans included in the analysis, 164,315 (45%) displayed symptoms of Post-Acute Sequelae of COVID-19 (PASC) 30 to 180 days following an acute infection with COVID-19. The Veterans in this analysis were predominantly male, non-Hispanic White, under the age of 65 years old, and lived in an urban residence. The strongest sociodemographic predictors for PASC included Hispanic ethnicity compared to Non-Hispanic White race (aOR=1.08), being between the ages of 50 and 64 compared to ages 50 and below (aOR=1.17) and living in an urban residence compared to living in a rural residence (aOR=1.04). The strongest clinical predictors for PASC included: depression (aOR=1.33), diabetes (aOR=8.46), alcohol abuse (aOR=2.71), drug abuse (aOR=2.94), and severe acute infection (aOR=1.42).

Discussion: Results demonstrate potential health inequities for vulnerable individuals, as well as increased risk for individuals with pre-existing comorbidities. Future research is necessary to continue identifying risk factors and pathophysiology to reduce the burden of PASC. The prevalence of PASC provides estimates for future health care utilization. This can be used by healthcare professionals to develop strategies in preparation of higher utilization. Additionally, these sociodemographic, SDOH, and clinical risk factors can aid in public health interventions to reduce the burden of PASC for individuals who had COVID-19.

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I. Background

A. Introduction

Coronavirus disease (COVID-19) is a viral disease caused by SARS-CoV-2 that was declared an outbreak by the World Health Organization (WHO) in March 2020[1]. There has since been immense effort to identify risk factors, mechanisms, prevention measures, and treatments for acute SARS-CoV-2 infection.[2–4] However, an unexpected outcome from COVID-19 is post-acute sequelae– also referred to as long COVID. Following an acute infection, multi-organ and long-lasting symptoms have been reported, which has not been comprehensively described[5]. Considering the significant burden of disease[6], it is critical to identify risk factors and prevalence of post-acute sequelae to analyze the cost and consequences beyond an acute infection.

Reports of morbidity following a COVID-19 infection started appearing in late 2020[5,7–9]. One of the initial reports was a case series of multisystem inflammatory syndrome seen in adults following a COVID-19 infection. The findings indicated that adult patients may develop hyperinflammatory syndrome following a SARS-Cov-2 infection with no apparent differences based on severity of infection. The reports described in this case series demonstrate that individuals experienced cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms[7]. Additionally, multisystem inflammatory syndrome (MIS) was observed and reported in children. In a systematic review of MIS in children, the authors describe fever, gastrointestinal, cardiovascular, and mucocutaneous symptoms following COVID-19. Many of the cases also had elevated C-reactive protein, along with other biomarkers, suggesting a hyperinflammatory state[9].

Despite these initial reports in late 2020, it was not until October 2021 when the WHO released a clinical case definition of post COVID-19 condition. The clinical case definition of

post COVID-19 condition includes having symptoms developed within three months after infection with SARS-CoV-2. Common post-COVID-19 symptoms typically include fatigue, shortness of breath, and cognitive dysfunction. The name for this condition varies in the literature and has been called “long COVID,” “long-haul COVID,” “post-acute COVID-19 condition,” “post-acute sequelae of SARS-CoV-2 infection,” or “chronic COVID.”[10] For the purpose of this paper, we will refer to the condition as “post-acute sequelae of COVID-19 (PASC)”. Defining this condition established a framework for future studies to help identify risk factors, mechanisms, clinical characteristics, and treatments. However, further characterization of post-acute COVID-19 condition is needed to increase the sensitivity of the case definition. Additionally, the Centers for Disease Control and Prevention’s National Center for Health Statistics (CDC/NCHS) implemented a code into the International Classification of Diseases, Tenth Revision (ICD-10) to denote a post COVID-19 condition (U09.9) in October 2021[11].

There are a wide range of estimates on the prevalence of PASC, which could be explained by the variance in definitions and follow-up time. One meta-analysis of 63 studies from 22 countries in different world regions examined the prevalence of PASC at different follow-up times. The prevalence of at least one symptom was estimated to be 63.2% at 30 days after COVID-19 symptom onset. The prevalence of at least one symptom was estimated to be 71.9% at 60 days after symptom onset, and a prevalence of 45.9% at 90 days after symptom onset. The highest prevalence for symptoms was fatigue and dyspnea, and this ranged from 35 to 60% depending on the follow-up time[12]. Conversely, a symptom-tracking study in the United Kingdom estimated the prevalence of PASC among 4,182 individuals and found that 13% of individuals self-reported symptoms after one month of COVID-19 symptom onset and 4.5% at two months[13]. Further research is needed to accurately understand the prevalence of PASC.

B. Symptoms

1. Pulmonary

PASC, symptoms appearing four weeks after the onset of symptoms, has been observed in every organ system[14]. Lung abnormalities following COVID-19 have been reported by patients within one to nine months after symptom onset[15–20]. One of the most common persistent symptoms following acute COVID-19 is dyspnea, which was defined as shortness of breath. In a meta-analysis of 28 studies and 8,132 patients, 25% of patients experience dyspnea between three to six months following COVID-19. Further, the same 25% of patients continued to experience dyspnea between six to nine months post-COVID[15]. Another common lung manifestation is the alterations of pulmonary function tests (PFTs). In a cohort study of 2,469 patients discharged from a hospital in Wuhan, China, long-term pulmonary consequences were described. Patients who experienced a severe case of COVID-19 had increased risk of pulmonary diffusion abnormalities seen in the PFTs[20].

One of the more severe post-COVID lung conditions is the development of acute respiratory distress syndrome (ARDS) and pulmonary fibrosis. This was an expected outcome from COVID-19 due to it being a known outcome for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[21]. In a prospective cohort study of 1,099 patients in Wuhan, China, 3.4% of cases developed ARDS and 15% of severe cases developed ARDS.[22] However, this study did not follow patients who developed ARDS to see if they also developed pulmonary fibrosis, which is typically a secondary diagnosis.

2. Hematologic

Hematologic conditions such as thrombosis and ischemic stroke, have been well documented as post-COVID-19 outcomes[23–27]. In a matched cohort study of national registries in Sweden,

incidence rates for deep vein thrombosis increased following 70 days after COVID-19. Additionally, incidence rates for pulmonary embolism increased in the following 110 days after COVID-19[28]. Similar conclusions were made in a meta-analysis of 91 studies and 35,017 patients testing positive for COVID-19. This study noted venous thromboembolism was a significant risk for patients following a severe case of COVID-19. They also reported a prevalence of thromboembolism to be 12.8%[26]. Another meta-analysis of 66 papers reported the prevalence of venous thromboembolism to be 7.9% in non-ICU patients and 22.7% in ICU patients[24]. Another reported hematologic manifestation of post-acute COVID-19 is ischemic stroke. In a cohort study of 3,334 hospitalized COVID-19 patients in New York City, 1.6% of patients had an ischemic stroke. Additionally, 16% of patients had a thrombotic event[29]. However, further research is needed to understand how the frequency and risk of thrombotic events post-COVID-19 compare in patients with mild illness.

3. Cardiovascular

The impact of PASC on the cardiovascular system has been reported in various cohort studies. The symptoms and conditions range from mild to severe and include, chest pain, myocarditis, arrhythmia, heart failure, and pericarditis[20,30–36]. In a cohort study of 3,011 patients across 13 countries, 12% of patients experienced cardiac complications following acute COVID-19. Myocarditis was one of the least common complications and occurred in about 0.1% of patients. Similarly, pericarditis was rare and only reported in 0.03% of patients[31]. In a systematic review of cardiovascular conditions post-acute COVID-19, many of the included studies noted increased incidence of arrhythmia. These studies also reported increased incidence of persistent symptoms such as, chest pain, increased resting heart rate, and palpitations[36].

4. Neuropsychiatric

COVID-19 survivors have reported chronic and persistent symptoms of fatigue, brain fog, psychiatric changes, and sleep disorders[37–42]. In a cohort study of 153,848 veterans in the United States, incident mental health disorders increased following 30 days after COVID-19 compared to veterans who did not test positive for COVID-19. The risk was highest among individuals who were hospitalized, however, the risk remained significantly high even among those with a mild infection. Additionally, there was an increased risk of being prescribed medications for depression and anxiety following an infection[41]. Another frequently observed condition following infection is sleep disturbances and insomnia. In a cross-sectional study of 500 post-COVID-19 patients revealed that 27% of patients experienced clinical insomnia and 59% of patients experienced subthreshold insomnia[42].

5. Renal

The development of acute kidney injury is a common presentation for severe acute COVID-19 as well as for post-COVID-19 outcome. A cohort study in the United States of 2,469 patients observed that patients who developed acute kidney injury during COVID-19 hospitalization had a higher percentage of eGFR decrease following one year after symptom onset. Furthermore, these individuals had an increased risk of a reduction in renal function and proteinuria compared to the patients that did not develop acute kidney injury during hospitalization[43].

6. Gastrointestinal

Some of the enteric symptoms reported following an acute infection with SARS-CoV-2 include loss of appetite, nausea, diarrhea, vomiting, and abdominal distension. In a retrospective cross-sectional study of patients hospitalized with COVID-19, patients were interviewed 90 days after hospitalization to assess gastrointestinal symptoms. To help reduce bias, the researchers

excluded any symptoms that were experienced prior to hospitalization. Loss of appetite was the most frequently reported symptom with 24% of patients experiencing this. In addition, patients experienced nausea, acid reflux, and diarrhea[44]. The prevalence of gastrointestinal symptoms following an infection have been estimated to be 22% by a meta-analysis of 50 studies. The five most common symptoms were loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain. There was no significant difference in the odds of experiencing gastrointestinal symptoms between mild versus severe cases of COVID-19. However, an important limitation to this study is that there was significant heterogeneity for some of the analyses[45].

7. Endocrine

Diabetes diagnosis following COVID-19 has been cited as a possible future health burden[46,47,48]. In a cohort study of 181,280 veterans who tested positive for COVID-19 and 4,118,441 controls, individuals with COVID-19 had an increased risk of incident diabetes and antihyperglycemic use. In addition, patients with a low risk of diabetes prior to COVID-19 had an increased risk for incident diabetes following an infection[46]. In addition to an increase in incident diabetes following COVID-19, there is emerging evidence to suggest an increase in incidence of thyroid disorders[47,48]. In a cohort study of 248 patients, researchers concluded that the number of patients with hypothyroidism in 2020 and 2021 was significantly higher than in 2019. However, there were no changes in the average dosage of levothyroxine between 2019, 2020, and 2021. The average time to hypothyroid diagnosis post-COVID-19 onset was three months for women and two months for men[47]. This can help guide future studies when assessing the time to PASC development[47].

B. Risk Factors

Possible risk factors for PASC include specific sociodemographic characteristics, COVID-19 vaccination status, SARS-CoV-2 variant, presence of comorbidities, and severity of initial infection[49–54]. However, the evidence for these risk factors is mixed. In a cross-sectional study of 274 individuals with COVID-19, individuals of older age and severe illness were found to be more likely to have persistent symptoms following acute infection[52]. Conversely, in a prospective cohort study of 1,038 US adults, researchers suggested that hospitalization for COVID-19, having diabetes, having a high BMI were independently associated with PASC development. This study found no differences in age, race/ethnicity, or Social Vulnerability Index for developing PASC[54]. In a large UK-based cohort of 486,149 adults, researchers determined female sex, being an ethnic minority, younger age group, socioeconomic deprivation, and various comorbidities to be associated with PASC[53]. There is a strong need for future research to identify risk factors so targeted intervention strategies may be implemented.

There is limited evidence examining how the risk of PASC development is impacted by the variants of SARS-CoV-2. One case-control observational study of 56,003 omicron strain cases and 41,361 delta strain cases, found a reduction in the odds of PASC with the omicron variant compared to the delta variant. However, in this study, the strains were defined based on the time of infection and were not laboratory confirmed. Future studies should consider cases confirmed by lab testing to reduce bias[55].

C. Veteran Population

There have been few studies examining PASC in the US Veteran population[34,35,41,56,57]. The US Department of Veterans Affairs (VA) electronic health databases offers robust data relating to COVID-19 and individual level patient sociodemographic. One investigation used VA

electronic health data to comprehensively described PASC symptoms. The risk of death for individuals surviving 30 days after an acute SARS-CoV-2 infection increases. In addition, these patients had increased utilization of healthcare resources and an increased risk of incident pulmonary and extrapulmonary diagnoses[35]. This paper examines over 379 incident diagnoses and demonstrates the range of symptoms for PASC, however, it does not look at risk factors. It is also important to note that this study occurred prior to the release of a clear definition and an ICD-10 code for PASC. In another cohort study utilizing the VA electronic health records, to explore the burden of PASC stratified by demographics, severity of infection, and baseline health status. At six months post-acute infection, the investigators report an estimated PASC burden of 73.43 per 1000 persons. The burden was increased in individuals with poorer baseline health and in individuals who had a more severe acute infection[56].

In addition to examining the characterization and burden of PASC within the veteran population, investigators have explored how potential risk factors including vaccination status and treatment for acute COVID-19. In a cohort study of 33,940 veterans with breakthrough infections, the authors suggest that patients with a breakthrough infection have a higher risk of developing PASC compared to patients with no history of COVID-19[57]. However, with updated COVID-19 vaccination guidelines[58], future research should examine how risk of PASC development changes with number of vaccines received. Considering the evidence for a higher risk of PASC with a more severe infection, another cohort study examined the impact of treatment with Paxlovid on PASC risk in the veteran population. Compared to veterans that were not treated with Paxlovid, veterans who did receive treatment had a significant reduction in their risk of developing PASC[59]. Lastly, in a retrospective cohort study of 198,601 US Veterans, researchers examined potential risk factors associated with the documentation of COVID-19

related care 3 months after acute infection. The study suggested older age, Black or American Indian/Alaska Native race, Hispanic ethnicity, urban residence, high Charlson Comorbidity Index score, and requiring hospitalization as potential risk factors[60]. However, one key limitation to this study is that the outcome of PASC was defined by documentation of the long COVID-19 ICD-10 code (U09.9). The true prevalence and risk factors may be underrepresented by not incorporating other documented symptoms.

D. Gaps in the Literature

Health officials are predicting a major health crisis as a direct result of post-acute COVID-19 outcomes; thus, further investigation is needed to determine at-risk populations[61]. While there is considerable evidence for the risk factors, mechanisms, and treatment for acute SARS-CoV-2 infection, there is limited literature about PASC. VA-specific research thus far has suggested systemic health conditions following an acute infection and shows an increased risk in individuals with severe acute infection[35,56]. There is a considerable need for research concerning the risk factors for PASC. Furthermore, the current VA-specific research utilizes the ICD-10 code for PASC. This may lead to an under-ascertainment of cases because it was not released until October 2021. In addition, it may not be inclusive of all possible post-acute sequelae.

E. Study Objectives

Considering the gaps and limitations of previous literature, this study aims to better understand PASC in the Veteran population. Specifically, this analysis has three main objectives. First, this analysis aims to determine the prevalence of PASC in the Veteran population. Second, we aim to identify key sociodemographic, SDOH, and clinical risk factors for PASC development. Lastly, the analysis will address how the risk of PASC changes based on time of infection.

III. Methods

A. Study Population and Study Design

A retrospective cohort study of Veterans within the United States Department of Veterans Affairs (VA) electronic health record network from March 1, 2020, to September 1, 2022, was conducted. All Veterans who had one hospital inpatient stay or outpatient visit between January 1, 2018, and September 30, 2022, were eligible. Individuals with a positive COVID-19 test between March 10, 2020, and September 30, 2022, were included in the analysis. Patients who died during initial acute COVID-19 infection were excluded from the study. This study was approved by the Atlanta VA Institutional Review Board and was granted a waiver of informed consent.

B. Data Sources

The study utilized four data sources: 1) United States Veterans Eligibility Trends and Statistics (USVETS) which contains individual-level characteristics for social determinants of health variables; 2) COVID-19 Shared Data Resource (CSDR) for COVID-19 testing results; 3) The VA Corporate Data Warehouse (CDW) for clinical data, and 4) U.S. Census American Community Survey from 2014 through 2019 for individual-level geographic data.

C. Data Measures

1. Outcome Variable

The outcome of interest (PASC) was obtained from the CSDR and coded as a binary variable based on documentation of COVID-19 symptoms appearing 30 to 180 days following a positive SARS-CoV-2 test result. This was operationally defined as having either: 1) an ICD-10 code for post-Covid-19 condition (U09.9), or 2) having documentation of at least one pre-specified symptoms 90 days following COVID-19. The prespecified symptoms include sequalae

from Cardiovascular, Dermatologic, Endocrine, Gastrointestinal, Neurologic, Pulmonary, and Musculoskeletal organ systems based on a review of the literature among VA and non-VA populations.

2. Exposure Variables

Demographic, SDOH, and clinical factors were each considered as individual exposures and are described in more detail below.

3. Demographic Variables

Demographic variables were obtained from the CDW and include age, sex, and race/ethnicity. Age was categorized into the following groups: 18 to 49 years old, 50 to 64 years old, 65 to 79 years old, and 80 years or older. Sex was reported as male or female. Race and ethnicity were combined and included the following categories: Non-Hispanic White, Non-Hispanic Black or African American, Asian, American Indian/ Alaska Native or Native Hawaiian/ other Pacific, or Hispanic/Latino.

4. SDOH Variables

SDOH variables were extracted from the USVETS database. Household income was categorized into three groups: less than $39,999, between $40,000 and $74,999, or greater than $75,000. Household size indicated the total number of individuals residing in the household including the respondent; it included four groups: 1 person, 2 people, 3 people, or four or more people. Educational level was categorized as: high school completion, college completion, completion of graduate school, and attendance to a technical or vocational school. Residence type was coded as rural or urban. Rural/urban residence was defined by the rural-urban commuting area codes[62].

5. Clinical Characteristics

Comorbid conditions and the Elixhauser Comorbidity index[63] were based on ICD-10 diagnostic codes and extracted from the CDW. The following conditions were examined: asthma, cancer, chronic obstructive pulmonary disease, depression, diabetes, human immunodeficiency virus, hypertension, liver disease, myocardial infarction, obesity, peripheral vascular disease, and renal disease. COVID-19 vaccination status was categorized on number of mRNA vaccines as the following: 0 doses, 1 dose, 2 doses, or 3 doses. Veterans were considered fully vaccinated if they received at least 2 doses of the mRNA vaccine. Veterans that received one dose of mRNA vaccine were considered partially vaccinated, and veterans with 0 doses were considered unvaccinated.

The CSDR was utilized for COVID-19 severity data and was defined as severe or not-severe. Severe COVID-19 was defined as being hospitalized or admission to the ICU within 60 days of a positive COVID-19 test. Time of acute COVID-19 infection was used as a proxy for COVID-19 strain causing infection. To estimate which time period corresponded to COVID-19 strain, data from the Global Initiative on Sharing Avian Influenza Data (GISAID) ,was utilized[64]. Time of infection was categorized as the following: before June 20, 2020, to represent the ancestral strain; June 20, 2020, to October 31, 2020, to represent the alpha strain; November 1, 2020, through November 1, 2021, to represent the delta strain; and lastly, November 2, 2021, to September 30, 2022, to represent the omicron strain.

D. Statistical Analysis

A descriptive analysis was performed for Veterans who utilized care within the study period. Categorical variables were summarized as frequencies and percentages. Unadjusted bivariate analyses were used with chi-square and t-tests to explore associations between baseline characteristics and PASC. A p-value of <0.05 was considered statistically significant.

Multivariable logistic regression was utilized to examine the individual association of the variables of interest on the development of PASC. The pre-specified factors included in the model were demographics (age, sex, race/ethnicity), SDOH variables (education level, income, marital status, rural/urban, individuals in household), and clinical characteristics (vaccination, comorbidities, acute COVID-19 severity). A chunk test utilizing likelihood ratio and chi-square was performed to determine if there was significant interaction by COVID-19 time period of infection. Subsequently, backwards elimination with an alpha of 0.05 was used to reduce the model to variables independently associated with PASC. Odds ratios and their corresponding 95% confidence intervals were calculated. The predictive value of the model was assessed by calculating a c-statistic. All statistical analysis was conducted in SAS Enterprise Guide version 8.3 (SAS Institute, Cary, NC, US).

IV. Results

A total of 8,887,531 Veteran had at least one inpatient hospital stay or outpatient encounter between January 1, 2018, and September 30, 2022. There were 8,168,175 Veterans excluded from the study due to a lack of documentation on testing for COVID-19. An additional 39,698 were excluded from the study if they died after their index COVID-19 positive test. Lastly, 315,833 were excluded if they were missing any of the explanatory variables. The final analytical dataset included 363,825 Veterans who all had at least one documented case of COVID-19 and complete data. (Figure 1).

From the 363,825 Veterans who were included in the analysis, 164,315 (45%) displayed symptoms of PASC 30 to 180 days following an acute infection with COVID-19. The majority of Veterans in the study population were male (88%), non-Hispanic White race (71%), and under the age of 65 years old (54%). In addition, 198,960 (55%) completed high school, 148,809 (41%)

reported a household income between $40,000 and $74,999, and 298,250 (82%) resided in an urban residence (Table 1).

Table 2 reports the baseline clinical characteristics for the 363,825 Veterans included in the analysis. There was a high prevalence of pre-existing comorbidities with depression (33%), diabetes (30%), hypertension (59%), and obesity (23%) being the highest. Among the 363,825 Veterans that tested positive for COVID-19, 21,188 (5.8%) had a severe infection. The most prevalent time period of infection was between November 2021 and September 2022 (50%), which roughly corresponds to omicron as the predominant strain. Lastly, 113,235 (31%) of Veterans had no record of COVID-19 vaccination, 85,428 (23%) Veterans were fully vaccinated against COVID-19, and 145,367 (40%) were fully vaccinated and received one booster against COVID-19.

The results examining sociodemographic characteristics with multivariate logistic regression are reported in Table 3. After fully adjusting for sociodemographic and clinical factors, the following SDOH/sociodemographic factors were identified as significant: Non-Hispanic Black or African American race compared to White race (OR, 0.96; 95% CI, 0.94-0.98), Asian race compared to White race (OR, 0.92; 95% CI, 0.85-0.99), Hispanic ethnicity compared to Non-Hispanic White race (OR, 1.06; 95% CI, 1.03-1.10), ages 50-64 years compared to younger than 50 years (OR, 1.17; 95% CI, 1.14-1.20), ages 80 years or older compared to younger than 50 years (OR, 0.64; 95% CI, 0.61-0.66), completion of graduate school compared to completion of high school (OR, 0.96; 95% CI, 0.94-0.98), a household size of four or more people compared to one person (OR, 1.03; 95% CI, 1.01-1.06), income of $40,000 to $74,999 compared to less than $40,000 (OR, 0.98; 95% CI, 0.96-0.99), income of

$75,000 or more compared to less than $40,000 (OR, 0.92; 95% CI, 0.91-0.95), and urban residence compared to rural residence (OR, 1.04; 95% CI, 1.02-1.06).

The results for clinical risk factors associated with PASC, assessed by multivariate logistic regression, are reported in Table 4. After fully adjusting for sociodemographic and clinical factors, the following comorbidities were identified as significant compared to a disease-free state: Asthma (OR, 1.07; 95% CI, 1.03-1.10), COPD (OR, 1.10; 95% CI, 1.07-1.12), Depression (OR, 1.33; 95% CI, 1.30-1.35), Diabetes (OR, 8.46; 95% CI, 8.31-8.62), Heart Failure (OR, 1.14; 95% CI, 1.10-1.18), HIV (OR, 0.81; 95% CI, 0.73-0.89), Hypertension (OR, 1.16; 95% CI, 1.14-1.22), history of MI (OR, 1.18; 95% CI, 1.14-1.22), Obesity (OR, 1.13; 95% CI 1.11-1.15), PVD (OR, 1.15; 95% CI, 1.11-1.19), and Renal Disease (OR, 1.26; 95% CI, 1.23-1.30). In addition, history of alcohol abuse (OR, 2.71; 95% CI, 2.64-2.80), tobacco abuse (OR, 1.20; 95% CI, 1.17-1.24), and drug abuse (OR, 2.94; 95% CI, 2.83-3.06) were all significant. A severe COVID-19 infection compared to a mild or moderate infection (OR, 1.42; 95% CI, 1.29-1.43) and hospitalization from an acute infection (OR, 1.36; 95% CI, 1.24-1.48) both significantly increased the odds of developing PASC. The odds of developing PASC increased with the time period of infection. For instance, compared to an infection before June 20, 2020 (ancestral strain), the odds of developing PASC with an infection between June 20, 2020, and October 31, 2020 (alpha strain), was 1.25; the odds of developing PASC with an infection between November 1, 2020, and November 1, 2021 (delta strain), was 1.35; lastly, the odds of developing PASC with an infection between November 2, 2021, and September 30, 2022 (omicron strain), was 1.57. The odds of developing PASC significantly increased as the number of mRNA vaccine doses received increased (Table 4).

A significant interaction was detected between the time period of infection and diabetes, as well as between the time period of infection and number of mRNA doses received. The odds of developing PASC stratified by time of infection is presented in Table 5. The odds of developing PASC among individuals with diabetes increased as the time period of infection increased. The odds of developing PASC among individuals receiving any dose of mRNA vaccination decreased as the time period increased. In addition, the odds of developing PASC increased as the number of mRNA vaccine doses increased.

IV. Discussion

This study estimated the prevalence of PASC and identified sociodemographic, SDOH, and clinical risk factors for the development of PASC in the Veteran population. In addition, the study aimed to determine if the odds of PASC development varied by time period of COVID-19 infection. The results estimated the prevalence of PASC to be 45% of patients that reported an acute COVID-19 infection. Patients with pre-existing comorbidities, Hispanic ethnicity compared to white race, severe acute infection with COVID-19, and having an omicron or omicron-descendant infection were at an increased risk of developing PASC.

Our results demonstrated PASC prevalence to be 45%, which is consistent with the literature estimations for prevalence among U.S adults[13,65]. However, the results indicate a higher prevalence than found in a recent cohort study among Veterans in the U.S, which estimated prevalence to be 13.5%[60]. One important difference is that the current study utilized both documentation of the Post COVID condition ICD-10 code (U09.9) as well as documentation of conditions found to be associated with an acute SARS-CoV-2 infection. Considering that the ICD-10 code was not established until October 1, 2021, adding other diagnoses will capture a larger proportion of cases but may be less specific.

To our knowledge, current studies have not explored specific SDOH variables as risk factors for PASC development; however, our findings are consistent with literature suggesting socioeconomic deprivation increases risk of PASC development[53]. Those with Hispanic ethnicity experienced the highest odds of PASC development compared to non-Hispanic White race. The odds for PASC development decreased for non-Hispanic Black or African American, Asian, and American Indian/Alaska Native Veterans. This suggests that pre-existing comorbidities and SDOH factors may better explain this association. For instance, in another cohort study, adjusting for SDOH factors diminished the increased risk of PASC development among ethnic minorities[54].In addition to racial disparities in PASC development, our results suggest health inequities among individuals with lower income, urban residence, and lower education level.

Our findings that pre-existing comorbidities increased the risk of PASC development is consistent with much of the literature[46,49–51]. Diabetes, Depression, and renal disease were all associated with the highest odds of developing PASC. This knowledge adds to the existing evidence that future research should consider extrapulmonary conditions when examining PASC from COVID-19. In addition, the odds of PASC increased with any documentation of substance abuse, such as drug, alcohol, or tobacco. There is evidence that substance abuse increases the risk of adverse outcomes from COVID-19, such as hospitalization or death[66]. The results from this analysis add to the current literature by providing support for an increased risk of PASC among individuals that report substance abuse.

The results that a more severe SARS-CoV-2 infection increase odds of PASC supports the current literature[52,54]. In contrast, our findings are inconsistent with the literature suggesting delta strain infection has the greatest impact on increased risk of PASC[55,67]. However, the present

study utilized time period of infection as a proxy for infection strain, which may have biased the results. Lastly, our findings that mRNA vaccination prior to SARS-CoV-2 infection increased the odds of PASC were surprising and inconsistent with the literature[68–70]. Since the odds of PASC decreased after controlling for sociodemographic and clinical factors, there may have been other confounding variables not considered that could explain the increased odds observed. For instance, healthcare utilization may impact these results; individuals with increased healthcare visits may be more likely to be vaccinated as well as more likely to be diagnosed with PASC.

There are at least four strengths of this study. First, the study utilizes a large cohort from the US Department of Veterans Affairs, which makes the results generalizable to Veterans in the US who access healthcare. Second, to our knowledge, this is the first large study to incorporate specific SDOH variables in examining risk of PASC. Third, we leveraged previous literature on PASC to improve estimates of prevalence. For instance, many of the current studies utilize the U09.9 ICD-10 code alone, which may underreport the number of true cases. Lastly, the Veteran population is representative of a broad range of regions across the US. This allows for the examination of differences across geographic regions.

Despite these strengths, there are at least two limitations. First, a large amount of missing data for sociodemographic variables could bias the results. Second, Veterans who either receive their care outside of VA facilities or received COVID-19 testing outside of the VA were not included in the analysis. However, prior research demonstrates that VA healthcare utilization was about 48% in 2016 and continues to increase[71]. In addition, the impact of Veterans testing outside of VA facilities, would likely bias results towards the null if present. Lastly, the study does not consider subsequent positive tests beyond the index test.

The findings from this study highlight the critical need for further research. For instance, the results from this study suggest possible health inequities in PASC. A recent review emphasizes that long COVID may disproportionately impact vulnerable populations[72]. Future investigations into the risk factors, pathophysiology, and treatments for PASC are necessary to reduce the burden on individuals and healthcare systems. Second, more research is needed to understand the utilization of the PASC ICD-10 code (U09.9) by healthcare personnel. Depending on how the code is used, this may bias prevalence estimates. In addition, future studies should consider incorporating extrapulmonary conditions within their definition of PASC, as this may capture more cases when estimating prevalence. Finally, future analyses should examine lab-confirmed strain impacts on PASC in addition to the time period of infection. This could help address any differences observed on risk of PASC by strain of infection.

This study raises important implications for clinicians and patients. First, the estimation of PASC prevalence emphasizes the importance of the continued mitigation measures needed against COVID-19. Furthermore, considering the potentially high prevalence of PASC observed in this study as well as in prior research, health care systems should be informed and prepared for an increase in incident conditions following COVID-19. Second, the risk factors identified can inform clinicians and provide targets for public health interventions. Specifically, individuals with pre-existing comorbidities, Hispanic ethnicity, and severe acute infections with SARS-CoV-2 should be targeted to receive interventions due to their increased risk of PASC. The findings from this paper can serve as a springboard for future research into PASC risk factors and be used to inform population health initiatives to reduce health dipartites.

V. References

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VI. Figures and Tables

Figure 1: Consort diagram of patients tested for SARS-CoV-2 across nationwide VHA facilities between January 20, 2020, and September 30, 2022, with complete data.

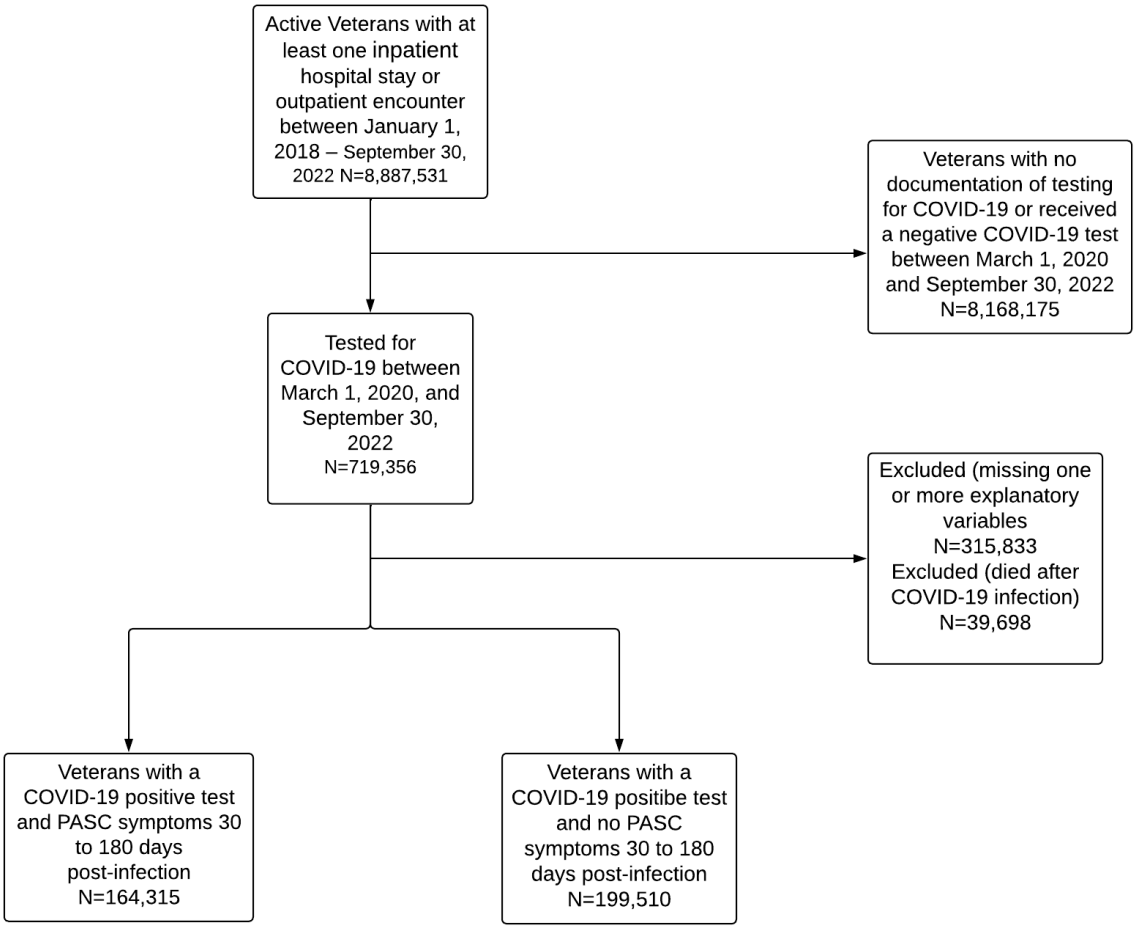

Table 1: Baseline Sociodemographic Characteristics of COVID-19 positive patients by evidence of PASC in national Veteran population, n = 363,825

Baseline Characteristics	No PASC 30-180 days following infection (n=199,510)		PASC 30-180 days following infection (n=164,315)		Chi-Square
	N	Percent	N	Percent	p-value
Gender					p<0.001
Male	172,372	86.4%	146,965	89.4%	
Female	27,138	13.6%	17,350	10.6%	
Race/Ethnicity					p<0.001
Non-Hispanic White	144,269	72.3%	114,924	69.9%	
Non-Hispanic Black or African American	39,124	19.6%	35,549	21.6%	
Asian	2,231	1.1%	1,696	1.03%	
American Indian or Alaska Native	1,363	0.7%	1,273	0.8%	
Hispanic	12,523	6.3%	10,873	6.6%	
Age					p<0.001
<50	59,324	29.7%	33,364	20.3%	
50-64	53,030	26.6%	51,174	31.1%	
65-79	68,064	34.1%	68,998	42.0%	
>80	19,092	9.6%	10,781	6.6%	
Education					p<0.001
Completed High School	109,731	55.0%	89,229	54.3%	
Completed College	65,176	32.7%	54,973	33.5%	
Completed Graduate School	22,417	11.2%	18,088	11.0%	
Attended Vocational/Technical School	2,186	1.1%	2,025	1.2%	
Household Size					p<0.001
1 person	46,863	23.5%	36,814	22.4%	
2 people	53,397	26.8%	43,317	26.4%	
3 people	47,445	23.8%	39,276	23.9%	
4 or more people	51,805	25.6%	44,908	27.3%	
Income					p<0.001
Less than $39,999	64,258	32.2%	55,099	33.5%	
$40,000 to $74,999	81,079	40.6%	67,730	41.2%	
$75,000 or more	54,173	27.1%	41,486	25.3%	
RUCA					p<0.001
Urban	164,096	82.3%	134,154	81.6%	
Rural	35,414	17.8%	30,161	18.4%	

Table 2: Baseline Clinical Characteristics of COVID-19 positive patients by evidence of PASC in national Veteran population, n = 363,825

Baseline Characteristics	No PASC 30-180 days following infection (n=199,510)		PASC 30-180 days following infection (n=164,315)		Chi-Square
	N	Percent	N	Percent	p-value
Comorbidities					
Asthma	12,748	6.4%	10,522	6.4%	p=0.865
Cancer	17,428	8.7%	17,178	10.5%	p<0.001
COPD	21,618	10.8%	24,086	14.7%	p<0.001
Depression	58,214	29.2%	60,049	36.6%	p<0.001
Diabetes	23,279	11.7%	85,207	51.9%	p<0.001
Heart Failure	10,884	5.5%	16,545	10.1%	p<0.001
HIV	1,248	0.6%	985	0.6%	p=0.316
Hypertension	103,296	51.8%	111,115	67.6%	p<0.001
Liver Disease	9,122	4.6%	12,991	7.9%	p<0.001
MI	3,483	1.8%	5,523	3.4%	p<0.001
Obesity	40,500	20.3%	44,472	27.1%	p<0.001
PVD	10,652	5.3%	13,706	8.3%	p<0.001
Renal Disease	15,928	8.0%	23,180	14.1%	p<0.001
Elixhauser Comorbidity Score					p<0.001
Less than 7	119,253	63.78%	67,734	36.2%	
7 or greater	79,047	51.5%	74,395	48.5%	
Substance Abuse					
Alcohol	9,514	4.8%	19,409	11.8%	p<0.001
Tobacco	12,736	6.4%	14,810	9.0%	p<0.001
Drug	5,132	2.6%	12,472	7.6%	p<0.001
Severity of Acute Infection					
Severe (vs. mild/moderate)	8,110	4.1%	13,078	8.0%	p<0.001
Hospital Admission	5,158	2.6%	9,166	5.6%	p<0.001
ICU Admission	4,077	2.0%	6,029	3.7%	p<0.001
Ventilator	14	0.01%	17	0.01%	p=0.286
Intubation	981	0.5%	705	0.4%	p=0.006
Time Period of Infection					p<0.001
Before June 20, 2020 (ancestral)	4,397	2.2%	3,069	1.9%	
June 20, 2020–October 31, 2020 (alpha)	16,794	8.4%	12,496	7.6%	
November 1, 2020–November 1, 2021(delta)	83,662	41.9%	63,217	38.5%	
November 2, 2021–September 30, 2022(omicron)	94,657	47.4%	85,533	52.1%	

mRNA Vaccine Doses Received					p<0.001
0	71,635	35.9%	41,600	25.3%	
1	11,221	5.6%	8,574	5.2%	
2	47,690	23.9%	37,738	23.0%	
3	68,964	34.6%	76,403	46.5%	

COPD: Chronic Obstructive Pulmonary Disease, HIV: Human Immunodeficiency Virus, MI: Myocardial Infarction, PVD: Peripheral Vascular Disease

Table 3: Sociodemographic Risk Factors Associated with the development of PASC, n = 363,825

	Univariate Logistic Regression		**Multivariate Logistic Regression[1]**	
Variables	**Odds Ratio**	**CI**	**Odds Ratio**	**CI**
Gender:				
Male	REF		REF	
Female	**0.75**	0.74-0.77	1.02	0.99-1.04
Race:				
White	REF		REF	
Non-Hispanic Black or African American	**1.14**	1.12-1.16	**0.96**	0.94-0.98
Asian	**0.95**	0.89-1.02	**0.92**	0.85-0.99
Hispanic	**1.09**	1.06-1.12	**1.06**	1.03-1.10
American Indian/Alaska Native	**1.17**	1.09-1.27	1.08	0.99-1.18
Age:				
<50	REF		REF	
50-64	**1.72**	1.69-1.75	**1.17**	1.14-1.20
65-79	**1.80**	1.77-1.83	0.99	0.97-1.02
>80	1.0	0.98-1.03	**0.64**	0.61-0.66
Education:				
Completed High School	REF		REF	
Completed College	**1.04**	1.02-1.05	1.01	0.99-1.03
Completed Graduate School	0.99	0.97-1.01	**0.96**	0.94-0.98
Attended Vocational/Technical School	**1.14**	1.07-1.21	1.02	0.95-1.10
Household Size:				
1 person	REF		REF	
2 people	**1.03**	1.01-1.05	1.01	0.99-1.03
3 people	**1.05**	1.03-1.07	1.03	1.00-1.05
4 or more people	**1.10**	1.08-1.12	**1.03**	1.01-1.06
Income:				
Less than $39,999	REF		REF	
$40,000 to $74,999	**0.97**	0.96-0.99	**0.98**	0.96-0.99
$75,000 or more	**0.89**	0.88-0.91	**0.92**	0.91-0.95
RUCA:				
Rural	REF		REF	
Urban	**1.04**	1.02-1.06	1.04	1.02-1.06
***C Statistic**			**c = 0.777**	

***Bold font indicates statistical significance**

[1]Adjusted for age, gender, race/ethnicity, education, income, household size, RUCA, comorbidities, substance abuse, severity of infection, time period of infection, and vaccination

Table 4: Clinical Risk Factors Associated with the development of PASC, n = 363,825

	Univariate Logistic Regression		Multivariate Logistic Regression[1]	
Variables	**Odds Ratio**	**CI**	**Odds Ratio**	**CI**
Comorbidities: "Disease-free" reference				
Asthma	1.00	0.98-1.03	**1.07**	1.03-1.10
Cancer	**1.22**	1.19-1.25	1.01	0.98-1.04
COPD	**1.41**	1.39-1.44	**1.10**	1.07-1.12
Depression	**1.40**	1.38-1.42	**1.33**	1.30-1.35
Diabetes	**8.15**	8.02-8.30	**8.46**	8.31-8.62
Heart Failure	**1.94**	1.89-1.99	**1.14**	1.10-1.18
HIV	0.96	0.88-1.04	**0.81**	0.73-0.89
Hypertension	**1.95**	1.92-1.97	**1.16**	1.14-1.22
Liver Disease	**1.79**	1.74-1.84	0.99	0.97-1.02
MI	**1.96**	1.88-2.04	**1.18**	1.14-1.22
Obesity	**1.46**	1.44-1.48	**1.13**	1.11-1.15
PVD	**1.61**	1.57-1.66	**1.15**	1.11-1.19
Renal Disease	**1.89**	1.85-1.93	**1.26**	1.23-1.30
Substance Abuse: "No record" reference				
Alcohol	**2.68**	2.61-2.74	**2.71**	2.64-2.80
Tobacco	**1.45**	1.42-1.49	**1.20**	1.17-1.24
Drug	**3.11**	3.00-3.22	**2.94**	2.83-3.06
Severity of Acute Infection				
Severe (vs. mild/moderate reference)	**2.04**	1.98-2.10	**1.42**	1.29-1.43
Hospital Admission	**2.23**	2.15-2.31	**1.36**	1.24-1.48
ICU Admission	**1.83**	1.75-1.90	0.95	0.87-1.03
Time Period of Infection:				
Before June 20, 2020 (ancestral)	REF		REF	
June 20, 2020 – October 31, 2020 (alpha)	**1.07**	1.01-1.12	**1.25**	1.18-1.33
November 1, 2020– November 1, 2021 (delta)	**1.08**	1.03-1.14	**1.35**	1.28-1.43
November 2, 2021 – September 30, 2022 (omicron)	**1.30**	1.24-1.36	**1.57**	1.48-1.70
mRNA Vaccine Doses Received:				
0 doses	REF		REF	
1 dose	**1.32**	1.28-1.34	**1.29**	1.24-1.33
2 doses	**1.36**	1.34-1-39	**1.35**	1.32-1.37
3 doses	**1.91**	1.88-1.94	**1.75**	1.71-1.78
***C Statistic**			**c = 0.777**	

***Bold font indicates statistical significance**

[1]Adjusted for age, gender, race/ethnicity, education, income, household size, RUCA, comorbidities, substance abuse, severity of infection, time period of infection, and vaccination

Table 5: Odds of Developing PASC stratified by Time of Infection

	Unadjusted n=363,825	**Overall[1] n=363,825**	**Before June 20, 2020[1](ancestral) n=7,466**	**June 20, 2020 – October 31, 2020[1](alpha) n=29,290**	**November 1, 2020–November 1, 2021[1] (delta) n=146,879**	**November 2, 2021-September 30, 2022[1](omicron) n=180,190**
Variables	**OR(95% CI)**	**OR(95% CI)**	**OR(95% CI)**	**OR(95% CI)**	**OR(95% CI)**	**OR(95% CI)**
Diabetes vs disease-free reference	8.15(8.02,8.30)	8.46(8.31,8.62)	6.47 (5.73,7.3)	7.72(7.25,8.21)	8.33(8.10,8.57)	9.03(8.79,9.27)
mRNA doses Received						
0	REF	REF	REF	REF	REF	REF
1	1.32(1.28,1.34)	1.29(1.24,1.33)	2.51(1.88,3.36)	1.56(1.38,1.78)	1.45(1.38,1.53)	1.04(0.99,1.10)
2	1.36(1.34,1.39)	1.35(1.32,1.37)	2.76(2.40,3.22)	1.73(1.60,1.86)	1.51(1.47,1.56)	1.09(1.06,1.13)
3	1.91(1.88,1.94)	1.75(1.71,1.78)	3.31(2.91,3.78)	2.20(2.06,2.35)	1.99(1.93,2.04)	1.41(1.37,1.45)
***C Statistic**		c=0.777	c=0.789	c=0.779	c=0.776	c=0.777

[1]Adjusted for age, gender, race/ethnicity, education, income, household size, RUCA, comorbidities, substance abuse, severity of infection, time period of infection, and vaccination