*Open Forum Infectious Diseases*

**MAJOR ARTICLE**

# Association of COVID-19 Vaccination with Risk of Medically-Attended Post-Acute Sequelae of COVID-19 During the Ancestral, Alpha, Delta, and Omicron Variant Eras

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**Background:** Uncertainty exists regarding the effectiveness of COVID-19 vaccine to prevent Post-Acute Sequelae of COVID-19 (PASC) following a breakthrough infection. While most studies using symptom surveys found an association between preinfection vaccination status and PASC symptoms, studies of medically attended PASC are less common and have reported conflicting findings.

**Methods:** In this retrospective cohort of patients with an initial SARS-CoV-2 infection, who were continually empaneled for primary care in a large US health system, the electronic health record was queried for pre-infection vaccination status, demographics, comorbidity index, and diagnosed conditions. Multivariable logistic regression was used to model the outcome of a medically-attended PASC diagnosis within 6 months of SARS-CoV-2 infection. Likelihood ratio tests were

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used to assess the interaction between vaccination status and prevalent variant at the time of infection, and between vaccination status and hospitalization for the SARS-CoV-2 infection.

**Results:** During the observation period, 6.9% of patients experienced medically-attended and diagnosed PASC. A diagnosis of PASC was associated with older age, female sex, hospitalization for the initial infection, and an increased severity-weighted comorbidity index, and was inversely associated with infection during the Omicron period. No difference in the development of diagnosed PASC was observed between unvaccinated patients, those vaccinated with 2 doses of an mRNA vaccine, and those with >2 doses.

**Conclusions:** We found no association between vaccination status at time of infection and subsequent development of medically diagnosed PASC. Vaccine remains an important measure to prevent SARS-CoV-2 infection and severity. Further research is needed to identify effective measures to prevent and treat PASC.

**Keywords:** Long COVID, Post-COVID conditions, Post-acute Sequelae of COVID-19, vaccination, SARS-CoV-2 infection, COVID-19 vaccine, mRNA vaccine

## BACKGROUND

Post-acute sequelae of SARS CoV-2 infection (PASC), also known as long-haul COVID or Long COVID-19 consists of symptoms that persist at least 3 months after the initial infection, although definitions have evolved over time [1-3]. The pathophysiologic basis of PASC has not yet been fully delineated [4]. While the severity of the initial infection is associated with the likelihood of developing PASC, PASC may occur in individuals with mild to moderate disease [5]. Therefore, on the population level, most PASC cases are caused by mild to moderate infections. Symptoms are numerous and highly variable and can cause significant functional impairment.

COVID-19 vaccine is known to be highly effective for prevention of symptomatic infection for several months, with continued long-term protection against severe infection, hospitalization, and death [6]. This protection against the most severe infections seems robust even as new circulating variants have emerged [7], but less protection is offered against mild-moderate disease and breakthrough infections are common, particularly as immunity wanes and/or new variants emerge which escape vaccine-mediated immunity [8]. Previous studies have attempted to elucidate whether vaccination protects against the development of PASC following a breakthrough infection, with several systematic reviews finding an association between pre-infection vaccination and reduced likelihood of developing PASC [9-11]. However most such studies have used symptom surveys to identify PASC, which are subject to recall bias. Others have attempted to mine the electronic health record (EHR) for report of possible PASC symptoms [12-15]. However, these studies are also limited because PASC symptoms such as fatigue are common and nonspecific. Furthermore, the mention of a symptom in a clinical visit or clinical communication

does not mean the symptom prompted the patient to seek medical evaluation. Thus, little is known about the rate of developing PASC, much less whether medically attended PASC is mitigated for vaccinated patients with breakthrough infection. Clinical diagnosis codes have shown a high positive predictive value for meeting diagnostic criteria for PASC [16]. [17]

The purpose of this study was to assess the association between COVID-19 mRNA vaccination and development of medically attended and diagnosed PASC following a confirmed SARS-CoV-2 infection, using data extracted from the EHR.

## METHODS

This retrospective cohort study was conducted in a large healthcare system in the Midwestern United States. All patients ages 5 years or older as of February 1, 2021, with an initial positive SARS-CoV-2 polymerase chain reaction (PCR) test between February 1, 2021, when vaccine became available for senior and high risk patients and most healthcare workers, and December 31, 2022, when home antigen testing was felt to have surpassed PCR in the diagnosis of new cases in the health system, and who were empaneled with a primary care provider within the healthcare system, were eligible for inclusion. The outcome was a clinical encounter with diagnostic codes commonly used within the institution for PASC (B94.8, U09.9, Z86.16, B97.29) or a visit to the organization's designated PASC Clinic between 30 days and 6 months after the infection. Initially, providers were instructed to utilize code B94.8 for suspected PASC cases. When U09.9 became available, a system-wide provider communication recommended use of this code. A review of codes used in patients referred to the designated PASC clinic identified that Z86.16 and B97.29 were also in common use. Patients were excluded if they had a previous SARS-CoV infection, died or changed their primary care provider to another healthcare system (aka "loss of empanelment"), developed a second SARS-CoV-2 infection at least 30 days after the initial infection, were vaccinated with a non-mRNA COVID-19 vaccine or an incomplete mRNA series, or received any dose of COVID-19 vaccine between their infection date and the end of the observation period. In addition, patients without Minnesota Research Authorization were excluded.

Vaccination status was the primary exposure of interest, and was defined as unvaccinated, vaccinated (at least 2 weeks prior to the initial COVID-19 infection) with 2 mRNA vaccines or with > 2 mRNA vaccines. In addition to vaccination status, variables extracted from the medical record included age, sex, race, Charlson comorbidity index, and smoking status. Smoking status was defined as current smoker, former smoker, never smoker, or unknown. Each COVID-19 infection was defined by a positive PCR and categorized by the prevalent SARS-CoV-2 variant circulating in the upper Midwest on the date of the initial positive PCR, as follows: ancestral variant 2/1/21 through 4/14/21; Alpha, 4/15/21 through 7/8/21; Delta, 7/9/21 through 1/4/22; Omicron, 1/5/22 through 12/31/22.

**Statistical analysis**

Multivariable logistic regression models were used to model the outcome of medically attended and diagnosed PASC. The covariates included in these models are vaccination status at the time of the initial SARS-CoV-2 infection, and potential confounders for the association between vaccination and the outcome, including age, sex, race, hospitalization during the initial infection, variant period (Ancestral, Alpha, Delta, Omicron), the severity-weighted Charlson Comorbidity Index, and smoking status. Likelihood ratio tests were used to assess the interaction between vaccination status and prevalent variant at the time of infection, as well as between vaccination status and hospitalization for the SARS-CoV-2 infection. These interactions were assessed in the full model with all the above covariates, but the final model presented did not include smoking status due to a large number of missing values for this variable. The final model presented utilized a complete case analysis, whereby patients with missing values were not included. The analysis used R software v. 4.2 (R Core Team (2022), Vienna, Austria. URL https://www.R-project.org/).

This study was determined to be minimal risk and exempt from review by the Mayo Clinic Institutional Review Board, IRB #21-000967.

## RESULTS

Of 59,855 individuals with SARS-CoV-2 infection identified by PCR during the enrollment period, 41,652 patients met study criteria and were included in the analysis (Figure 1.) The mean age was 41 years, a majority (23,006, 55.2%) were female, and 37,325 (90.7%) were White (Table 1.) At the time of initial infection, 9,744 (23.4 %) were vaccinated with 2 doses of mRNA vaccine and 7,658 (18.4 %) had received >2 mRNA doses. Most infections occurred during the Delta and Omicron eras (16,538 (39.8%) and 19,605 (47.1%) respectively) and only 8.2% required hospitalization. Of those with documentation of smoking status, two-thirds had never smoked. However smoking status was not documented for 70% of the patients (Table 1.) Overall, 2,888 patients (6.9%) received a diagnosis of PASC during the observation period (one to 6 months following their infection date). Table 2 shows the relationship between vaccination status and long COVID, stratified by COVID-19 variant.

In the multivariable analysis, no difference in medically-attended and diagnosed PASC was observed between unvaccinated patients, those vaccinated with 2 doses of an mRNA vaccine (aOR 0.98, p=0.7), and those with >2 doses (aOR 1.10, p=0.14) (Table 3). Additionally, no interaction was found between vaccination status and predominant circulating SARS-CoV-2 variant (p=0.79) or between vaccination status and hospitalization for the initial infection (p=0.16).

The development of medically attended and diagnosed PASC following a SARS-CoV-2 infection was associated with increasing age (aOR 1.17 per decade, p<0.001), female sex (aOR 1.51, p<0.001), non-ICU or ICU hospitalization for the initial infection (aOR 10.1, p<0.001 and aOR

11.0, p<0.001 respectively), and an increased severity-weighted comorbidity index (aOR 1.05 per increase of 1, p<0.001) (Table 3.) PASC was inversely associated with acquisition of SARS-CoV-2 infection during the Omicron period (aOR 0.67, p<0.001).

Smoking status was not associated with PASC for former and current smoking, (unadjusted OR 1.02, p=0.80 and 1.06, p=0.60 respectively) relative to never smoking.

## DISCUSSION

In this large cohort of empaneled primary care patients, we found no association between vaccination status at the time of a SARS-CoV-2 infection and the subsequent development of medically attended and diagnosed PASC. While most other studies have found a small to moderate association, with a lower incidence of PASC among previously vaccinated individuals, most study designs rely upon self-reported symptom surveys rather than a clinician's diagnosis [9-11]. In a systematic review, 7 of 9 studies on vaccination for the prevention of PASC used a symptom survey to classify PASC [10]. Of the two studies using an EHR to identify PASC, one found a minimal reduction in PASC risk among vaccinated patients, concluding that vaccine can only provide partial protection [12]; the other found no association between vaccination and PASC [14]. Other investigators using EHR analysis have found associations using reported symptoms or symptom-based diagnosis codes. One study found associations between vaccination and a lower risk of myriad conditions such as hypertension, diabetes, and thyroid disorders as well as common nonspecific symptoms such as fatigue, myalgias, headache, and gastrointestinal symptoms, but did not include cognitive complaints ("brain fog"), autonomic symptoms, or a PASC diagnosis [15]. Another classified patients as having PASC using a proprietary symptom analysis; less than 2% of patients developed PASC, suggesting low sensitivity for this diagnostic approach [13]. Tannous and colleagues found that vaccination was associated with a 42% reduction in likelihood of any constitutional symptom persisting more than 28 days after infection, a definition that may be overly broad [18].

Our findings are similar to those of Taquet and colleagues, who queried a large EHR network and used diagnostic codes to identify PASC. In their propensity matched cohorts of vaccinated and unvaccinated patients, they found many associations between vaccination and severity of infection, but no association with features of PASC [14]. Similarly, Durstenfeld et al found no association between vaccination status and development of at least one persistent PASC symptom following infection [19], and the RECoVERED prospective cohort study found no difference in symptoms or odds of full recovery among matched pairs of vaccinated and unvaccinated patients with PASC [20].

During the Omicron period, we observed a lower risk of developing PASC regardless of vaccination status, consistent with other recent analyses [21]. This may reflect changing virulence of the virus and the routine use of antiviral medication in individuals at high risk for severe

infection, resulting in lower hospitalization rates. We found no interaction between vaccination status and circulating variant, arguing against prior vaccination as a major contributor to lower morbidity associated with Omicron infections. Immunity from prior undiagnosed infection could play a role in mitigating the severity of Omicron infections, since a larger portion of the population had been infected by this time. The associations we observed between PASC and female sex, age, hospitalization (as a proxy for severity of infection), and comorbidities are consistent with those identified previously [22, 23].

The differences between our observations and those of other studies are most likely attributable to the defined outcome of interest and method of capturing the outcome. A strength of this study is the defined population remaining empaneled within the primary care practice in the health system throughout the observation period. This allows robust capture of medically documented outcomes. This is the primary respect in which our study design differs from the diagnostic code arm of the RECOVER trial, which is the published study most like ours [17]. Using this "captive primary care population" approach, we found nearly triple the incidence of medically attended and diagnosed PASC identified using the same diagnostic criteria as RECOVER. This may reflect greater capture of medical encounters with the local primary care providers compared to encounters with the academic medical center conducting the study. Our study may have thus identified more mild to moderate cases with symptoms that are bothersome enough to seek medical evaluation but not requiring referral to a specialist or designated PASC clinic. In fact, adding completion of a clinical encounter at a designated PASC Clinic to our outcome definition only added one patient not already identified by diagnosis code. Another possible explanation could be a more consistent use of ICD codes for suspected PASC due to the uniformity of coding instruction provided to all providers as employees of a single health system.

Compared to most other studies, we observed a lower rate of PASC overall. This is most likely due to choosing the outcome of medically attended and diagnosed PASC rather than a symptom survey, as most other studies have used. In addition to providing simplicity and clarity for a condition with multiple disparate and nonspecific symptoms, medical record documentation is more likely to exist for patients who are experiencing symptoms that impact their ability to function normally. This design also avoids the risk of recall bias inherent in symptom surveys and self-reported vaccination status. In one study, medical diagnosis codes had a positive predictive value of 94% for PASC [16], although this has not been validated in the US, and there is evidence that diagnosis codes for PASC are used more commonly in female and white patients, and among patients from areas of low poverty and low unemployment[24]. We utilized the two most commonly utilized diagnostic codes for PASC in the US, and added additional codes based on local practice norms. Cases may have been misclassified if the provider used a different code entirely. If providers were less inclined to use a PASC code in vaccinated patients, our results would be biased towards suggestion of a protective effect of vaccination.

Because we were interested in PASC cases likely to be associated with significant socioeconomic impact, we did not define our outcome using individual symptoms or symptom-based codes. One

study of individual symptoms documented in the EHR found that anosmia, hair loss, sneezing, ejaculation difficulty, and reduced libido had the strongest association with prior COVID-19 infection [25]. Although clinically important, these symptoms are unlikely to impact work or school attendance.

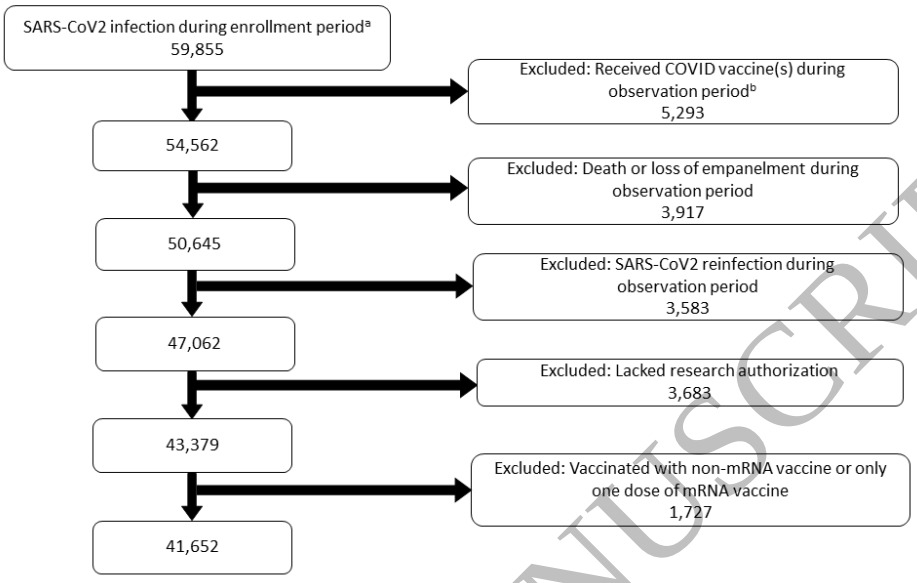
Throughout the study period, the health system periodically queried state immunization registries to actively incorporate externally-administered vaccines into the EHR, minimizing risk of misclassifying vaccinated patients. Other strengths of this study include its large size, broad age range, and a study period that spans four eras of circulating variant predominance. Since most infections occurred during the Delta and Omicron eras, when both infection severity and vaccine effectiveness had changed since the ancestral variant, findings are likely to be more applicable to the current state.

Consistent with the local population in the upper Midwest, over 90% of our patients were White, limiting generalizability to other races/ethnicities that are known to have not only more severe medical outcomes following SARS-CoV-2 infection but also lower vaccination rates and barriers to healthcare. Additionally, we did not seek to evaluate the role of hybrid immunity or multiple infections, association of vaccination with severity of subsequent PASC symptoms, or development of prolonged symptoms not requiring medical care. We excluded individuals with a second infection during the observation period which limits generalization somewhat to that population. The use of diagnosis codes could have introduced bias if their utilization changed over time along with vaccine-mediated immunity and changes in circulating variants; this risk may be mitigated somewhat in this setting where all providers were consistently advised regarding coding of PASC. By the end of 2022 home antigen tests had become the most common method of initial diagnosis and were inconsistently documented in the medical record. As the year progressed, we were able to detect a smaller proportion of new infections, which may have introduced selection bias if patients getting a PCR test had a higher risk of PASC. In this case the true risk of medically-attended and diagnosed PASC during the Omicron variant predominant timeframe may have been even lower than reflected in our data.

## CONCLUSIONS

While vaccination remains an important and effective tool to prevent SARS-CoV-2 infection, breakthrough infections will occur. We found no association with vaccination status at time of infection and the subsequent development of medically attended and diagnosed PASC. Individuals should maintain currency with COVID-19 vaccination to prevent infection and reduce severity of infection. Further research is needed to identify effective means of preventing and treating PASC.

Figure 1. Patient screening and selection flowchart




[a]February 1, 2021 through December 31, 2022
[b]Within six months after the date of infection

Table 1. Patient characteristics by vaccination status at time of SARS-CoV-2 infection

| | unvaccinated (N=24250) | 2 mRNA doses (N=9744) | >2 mRNA doses (N=7658) | Total (N=41652) |
|---|---|---|---|---|
| Age | | | | |
| Mean (SD) | 37.3 (21.3) | 40.8 (20.3) | 53.2 (19.9) | 41.0 (21.6) |
| 0-17 | 5566 (23.0%) | 1415 (14.5%) | 120 (1.6%) | 7101 (17.0%) |
| 18-39 | 8346 (34.4%) | 3597 (36.9%) | 2180 (28.5%) | 14123 (33.9%) |
| 40-64 | 7221 (29.8%) | 3391 (34.8%) | 2884 (37.7%) | 13496 (32.4%) |
| 65+ | 3117 (12.9%) | 1341 (13.8%) | 2474 (32.3%) | 6932 (16.6%) |
| Sex | n (%) | n (%) | n (%) | n (%) |
| Missing | 8 | 0 | 2 | 10 |
| Male | 11438 (47.2) | 4077 (41.8) | 3121 (40.8) | 18636 (44.8) |
| Female | 12804 (52.8) | 5667 (58.2) | 4535 (59.2) | 23006 (55.2) |
| Race | | | | |
| Missing | 293 | 116 | 74 | 483 |
| White | 21753 (90.8) | 8609 (89.4%) | 6963 (91.8%) | 37325 (90.7%) |
| Asian | 529 (2.2) | 364 (3.8%) | 344 (4.5%) | 1237 (3.0%) |
| Black | 1065 (4.4) | 416 (4.3%) | 171 (2.3%) | 1652 (4.0%) |
| Other | 610 (2.5) | 239 (2.5%) | 106 (1.4%) | 955 (2.3%) |
| COVID-19 variant era | | | | |
| Ancestral | 4373 (18.0) | 30 (0.3) | 0 (0.0) | 4403 (10.6) |
| Alpha | 991 (4.1) | 70 (0.7) | 0 (0.0) | 1061 (2.5) |
| Delta | 10908 (45.0) | 4840 (49.7) | 835 (10.9) | 16583 (39.8) |
| Omicron | 7978 (32.9) | 4804 (49.3) | 6823 (89.1) | 19605 (47.1) |
| Hospitalization | | | | |
| No | 22119 (91.2) | 9188 (94.3) | 6939 (90.6) | 38246 (91.8) |
| Hosp, No ICU | 1543 (6.4) | 408 (4.2) | 503 (6.6) | 2454 (5.9) |
| Hosp, ICU | 588 (2.4) | 148 (1.5) | 216 (2.8) | 952 (2.3) |
| Smoking Status | | | | |
| Missing (unknown) | 16655 | 6818 | 5789 | 29262 |
| Never | 5051 (66.5) | 1993 (68.1) | 1270 (68.0) | 8314 (67.1) |
| Former | 1471 (19.4) | 626 (21.4) | 486 (26.0) | 2583 (20.8) |
| Current | 1073 (14.1) | 307 (10.5) | 113 (6.0) | 1493 (12.1) |
| Charlson Index, severity weighted | | | | |
| Mean (SD) | 0.6 (1.6) | 0.7 (1.7) | 1.3 (2.4) | 0.8 (1.8) |

[a]Abbreviations: SD = Standard deviation; ICU = Intensive care unit

Table 2. Distribution of PASC[a] Cases by Predominant SARS-CoV2 Variant and Vaccination Status

| | | Vaccination Status | | |
|---|---|---|---|---|
| **Predominant Variant Era[b]** | **PASC Classification** | **unvaccinated (N=24250)** | **2 mRNA doses[c] (N=9744)** | **>2 mRNA doses[c] (N=7658)** |
| Ancestral | Total Patients | 4373 | 30 | 0 |
| | PASC | 353 (8.1%) | 3 (10.0%) | 0 |
| | No PASC | 4020 (91.9%) | 27 (90.0%) | 0 |
| Alpha | Total Patients | 991 | 70 | 0 |
| | PASC | 70 (7.1%) | 9 (12.9%) | 0 |
| | No PASC | 921 (92.9%) | 61 (87.1%) | 0 |
| Delta | Total Patients | 10908 | 4840 | 835 |
| | PASC | 731 (6.7%) | 385 (8.0%) | 77 (9.2%) |
| | No PASC | 10177 (93.3%) | 4455 (92.0%) | 758 (90.8%) |
| Omicron | Total Patients | 7978 | 4804 | 6823 |
| | PASC | 518 (6.5%) | 196 (4.1%) | 546 (8.0%) |
| | No PASC | 7460 (93.5%) | 4608 (95.9%) | 6277 (92.0%) |

[a]Abbreviation: PASC = Post Acute Sequelae of COVID-19

[b]Dates of variant predominance: Ancestral 2/1/21 - 4/14/21, Alpha 4/15/21 - 7/8/21, Delta 7/9/21 - 1/4/22, Omicron 1/5/22 - 12/31/22.

[c]Vaccinated at least 2 weeks prior to infection date.

Table 3. Multivariable logistic regression model for diagnosed PASC[a,b,c] (N=41,160)

| Characteristic | Total with PASC (%) | aOR | 95% CI | *p*-value |
|---|---|---|---|---|
| Age, per 10 yrs | | 1.17 | 1.14, 1.19 | <0.001 |
| 0-17 | 110 (1.6%) | | | |
| 18-39 | 730 (5.2%) | | | |
| 40-64 | 984 (7.4%) | | | |
| 65+ | 1033 (15.0%) | | | |
| Sex | | | | |
| Male | 1100 (6.0%) | — | — | |
| Female | 1757 (7.7%) | 1.51 | 1.38, 1.64 | <0.001 |
| Race | | | | |
| White | 2639 (7.1%) | — | — | |
| Asian | 67 (5.4%) | 1.07 | 0.81, 1.39 | 0.6 |
| Black | 99 (6.0%) | 1.07 | 0.85, 1.33 | 0.5 |
| Other | 52 (5.5%) | 1.01 | 0.74, 1.36 | >0.9 |
| COVID-19 variant era | | | | |
| Ancestral | 351 (8.1%) | — | — | |
| Alpha | 78 (7.4%) | 0.90 | 0.67, 1.18 | 0.5 |
| Delta | 1179 (7.2%) | 0.97 | 0.84, 1.12 | 0.7 |
| Omicron | 1249 (6.5%) | 0.67 | 0.58, 0.78 | <0.001 |
| Hospitalization for COVID-19 | | | | |
| No | 1567 (4.1%) | — | — | |
| Hospitalized, No ICU | 909 (37.4%) | 10.1 | 9.06, 11.2 | <0.001 |
| Hospitalized, ICU | 381 (40.3%) | 11.0 | 9.43, 12.8 | <0.001 |
| Charlson index, severity weighted, per increase of 1 | 1337 (4.5%) | 1.05 | 1.03, 1.07 | <0.001 |
| 0 | 1520 (13.6%) | | | |
| ≥1 | | | | |
| Vaccination status at time of SARS-CoV2 infection | | | | |
| Unvaccinated | 1654 (6.9%) | — | — | |
| 2 mRNA doses | 584 (6.1%) | 0.98 | 0.87, 1.09 | 0.7 |
| >2 mRNA doses | 619 (8.2%) | 1.10 | 0.97, 1.24 | 0.14 |

[a]Multivariable model included only the terms shown. Interaction terms with vaccination status and the main effect of smoking were not included in this model for presentation purposes

[b]Abbreviations: PASC = Post Acute Sequelae of COVID-19, aOR = adjusted Odds Ratio, CI = Confidence Interval, ICU = Intensive care unit

[c]PASC diagnosed between 30 days and 6 months after infection

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