EFFECT OF PAXLOVID TREATMENT ON LONG COVID ONSET: AN EHR-BASED TARGET TRIAL EMULATION FROM N3C

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ABSTRACT

Preventing and treating post-acute sequelae of SARS-CoV-2 infection (PASC), commonly known as Long COVID, has become a public health priority. In this study, we examined whether treatment with Paxlovid in the acute phase of COVID-19 helps prevent the onset of PASC. We used electronic health records from the National Covid Cohort Collaborative (N3C) to define a cohort of 426,461 patients who had COVID-19 since April 1, 2022, and were eligible for Paxlovid treatment due to risk for progression to severe COVID-19. We used the target trial emulation (TTE) framework to estimate the effect of Paxlovid treatment on PASC incidence. Our primary outcome measure was a PASC computable phenotype. Secondary outcomes were the onset of novel cognitive, fatigue, and respiratory symptoms in the post-acute period. Paxlovid treatment did not have a significant effect on overall PASC incidence (relative risk [RR] = 0.99, 95% confidence interval [CI] 0.96-1.01). However, its effect varied across the cognitive (RR = 0.85, 95% CI 0.79-0.90), fatigue (RR = 0.93, 95% CI 0.89-0.96), and respiratory (RR = 0.99, 95% CI 0.95-1.02) symptom clusters, suggesting that Paxlovid treatment may help prevent post-acute cognitive and fatigue symptoms more than others.

INTRODUCTION

Post-acute sequelae of SARS-CoV-2 infection (PASC), commonly known as Long COVID, has become a public health priority. PASC affects people from all walks of life, and it is difficult to predict whether an individual will get PASC at the time of acute infection. Many people with PASC continue to feel the impacts of the disease years after infection. Mechanisms causing PASC remain largely unknown, and we have yet to identify a treatment that is consistently effective across the array of PASC manifestations. Therefore, developing effective PASC prevention strategies will be crucial to alleviating the long-term public health impact of COVID-19. There is an urgent need for research on this topic, including identifying novel interventions and assessing whether and how known interventions could help prevent PASC.

Nirmatrelvir with ritonavir (Paxlovid) was given an emergency use authorization (EUA) in the United States in December 2021 for the treatment of patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19. Paxlovid has proven effective at preventing severe COVID-19, hospitalization, and death, with supporting evidence from clinical trials and real-world evidence, although a recent study found that Paxlovid was less effective at preventing hospitalization from SARS-CoV-2 Omicron subvariants.[1–7]

In 2022, several teams published case reports where Paxlovid was used to treat PASC. Across three early reports, treatment was effective in five of six treated patients.[8–10] A larger 2023 report found mixed effects in 13 patients, suggesting that Paxlovid treatment "may have meaningful benefits for some people with Long COVID but not others".[11] In sum, this evidence motivated the RECOVER-VITAL trials to evaluate Paxlovid as a potential treatment for PASC.[12]

In addition to treating PASC, researchers have begun to explore whether Paxlovid treatment in the acute phase of COVID-19 infection could help prevent the onset of PASC. One plausible pathway could be reducing infection severity. Studies have found that more severe acute infection is associated with a higher risk of PASC.[13,14] In N3C, we have found that COVID-19-associated hospitalization is associated with a much greater likelihood of a PASC diagnosis.[15] A meta-analysis also found that hospitalized patients were more likely to have PASC.[16]

Few studies have explored Paxlovid as a PASC preventative, and results are mixed. The largest study to date (281,793 individuals) used data from the US Department of Veterans Affairs

(VA).[17] The VA study found that Paxlovid treatment during the acute phase of COVID-19 reduced the risk of a composite outcome of 13 post-acute sequelae, with a hazard ratio of 0.74.[17] However, two smaller studies found that Paxlovid treatment was not associated with a reduced risk of PASC: a survey of 4,684 individuals from the Covid Citizen Science cohort and a survey of 500 individuals from Montefiore Medical Center.[18,19] Although these studies are much smaller than the VA study, they are more representative of the general population, and survey methods may capture symptoms that EHR data do not. In sum, the relationship between Paxlovid treatment and PASC onset remains uncertain.

Through the National Institute of Health's National COVID Cohort Collaborative (N3C) , and as part of the RECOVER Initiative's EHR data team, we have the opportunity to study Paxlovid as a PASC preventative using a large, nationally sampled cohort.[20] We use the target trial emulation (TTE) framework to explicitly measure the effect of Paxlovid treatment in the acute phase of COVID-19 infection on the cumulative incidence of PASC.[21] We measure PASC incidence using a machine learning-based computable phenotype, which offers advantages over symptom-based outcomes[22]. As secondary outcomes, we also measure the novel onset of PASC symptoms in the cognitive, fatigue, and respiratory clusters proposed by the Global Burden of Disease program.[23] We conduct two sub-analyses: the first using a "VA-like cohort" designed to mirror the study period and demographics used in Xie et al. (2023)[17] and the second using data from the National Patient-Centered Clinical Research Network (PCORnet) database.

RESULTS

Patient Characteristics

After inclusion and exclusion criteria and within the study period, a total of 426,461 patients had a valid COVID-19 index date during the study period, of whom 123,209 (28.89%) were treated with Paxlovid, and 24,474 (5.74%) had PASC according to our primary outcome measure (U09.9 diagnosis or computable phenotype prediction over 0.9 from 29 to 180 days after index). After applying the eligibility criteria to the patient population and study sites, a total of 28 of 36 study sites were retained. The CONSORT flow diagram is shown in Figure 1. The characteristics of all patients during the study period are presented in Table 1, stratified by treatment group.

Figure 1: CONSORT Diagram: Study Cohort and Flow of Emulated Trial

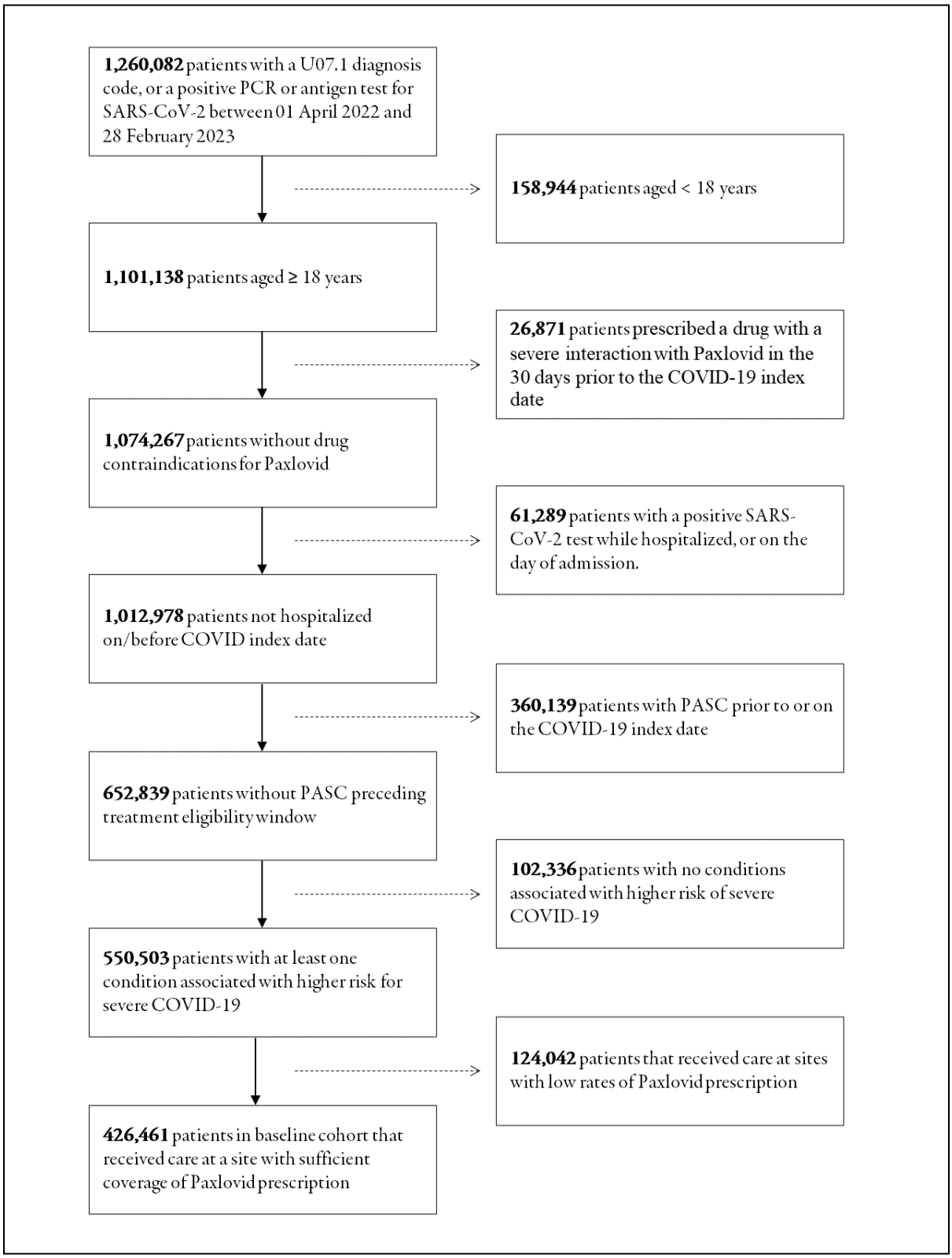


Table 1: Descriptive population characteristics within the N3C Cohort

Characteristic		Treatment Group	
		No Paxlovid (N=303,192)	Paxlovid (N=123,269)
PASC[1]			
	No	285,957 (94.3%)	116,030 (94.1%)
	Yes	17,235 (5.7%)	7,239 (5.9%)
Sex			
	Female	189,621 (62.5%)	74,634 (60.5%)
	Male	113,529 (37.4%)	48,615 (39.4%)
	Missing	42 (0.0%)	20 (0.0%)
Age (in years)			
	18-24	19,251 (6.3%)	2,913 (2.4%)
	25-34	41,954 (13.8%)	9,112 (7.4%)
	35-49	62,358 (20.6%)	22,282 (18.1%)
	50-64	84,869 (28.0%)	39,268 (31.9%)
	65+	94,760 (31.3%)	49,694 (40.3%)
Race and Ethnicity			
	Asian Non-Hispanic	13,621 (4.5%)	5,656 (4.6%)
	Black or African American Non-Hispanic	37,593 (12.4%)	11,903 (9.7%)
	Hispanic or Latino Any Race	32,539 (10.7%)	9,804 (8.0%)
	White Non-Hispanic	198,098 (65.3%)	88,307 (71.6%)
	Other Non-Hispanic	5,240 (1.7%)	1,389 (1.1%)
	Unknown	16,101 (5.3%)	6,210 (5.0%)
Charlson Comorbidity Index			
	0	165,583 (54.6%)	66,846 (54.2%)
	1-2	80,135 (26.4%)	38,615 (31.3%)
	3-4	22,124 (7.3%)	9,159 (7.4%)
	5-10	12,057 (4.0%)	4,029 (3.3%)
	11+	998 (0.3%)	289 (0.2%)
	Missing	22,295 (7.4%)	4,331 (3.5%)
Number of Visits in Prior Year			
	0	26,603 (8.8%)	6,391 (5.2%)
	1-3	52,041 (17.2%)	14,642 (11.9%)
	4-9	71,683 (23.6%)	29,348 (23.8%)
	10-20	75,434 (24.9%)	37,531 (30.4%)
	> 20	77,431 (25.5%)	35,357 (28.7%)
Number of Hospitalizations in Prior Year			
	0	2,997 (1.0%)	692 (0.6%)
	1	287,830 (94.9%)	119,009 (96.5%)
	> 1	12,365 (4.1%)	3,568 (2.9%)
Community Wellbeing Index[2]			
	0-45	2,194 (0.7%)	671 (0.5%)
	46-55	109,701 (36.2%)	37,098 (30.1%)
	56-65	137,979 (45.5%)	58,359 (47.3%)
	65+	22,131 (7.3%)	13,230 (10.7%)
	Missing	31,187 (10.3%)	13,911 (11.3%)
Month of COVID-19 diagnosis			
	April 2022	18,337 (6.0%)	3,807 (3.1%)
	May 2022	42,304 (14.0%)	13,081 (10.6%)
	June 2022	43,254 (14.3%)	14,962 (12.1%)
	July 2022	46,544 (15.4%)	18,696 (15.2%)
	August 2022	38,492 (12.7%)	15,144 (12.3%)
	September 2022	24,245 (8.0%)	10,039 (8.1%)
	October 2022	19,123 (6.3%)	7,411 (6.0%)
	November 2022	17,913 (5.9%)	8,533 (6.9%)
	December 2022	23,910 (7.9%)	14,465 (11.7%)
	January 2023	17,596 (5.8%)	9,740 (7.9%)
	February 2023	11,474 (3.8%)	7,391 (6.0%)

Notes: [1]Any PASC (CP or U09.9) between 28-days following a positive SARS-CoV-2 test result to 180 days post-index; [2]CWBI is a measure of five interrelated community-level domains: Healthcare access (ratios of healthcare providers to population), Resource access (libraries and religious institutions, employment, and grocery stores), Food access (access to grocery stores and produce), Housing & transportation (home values, ratio of home value to income, and public transit use), and Economic security (rates of employment, labor force participation, health insurance coverage rate, and household income above the poverty level).[24]

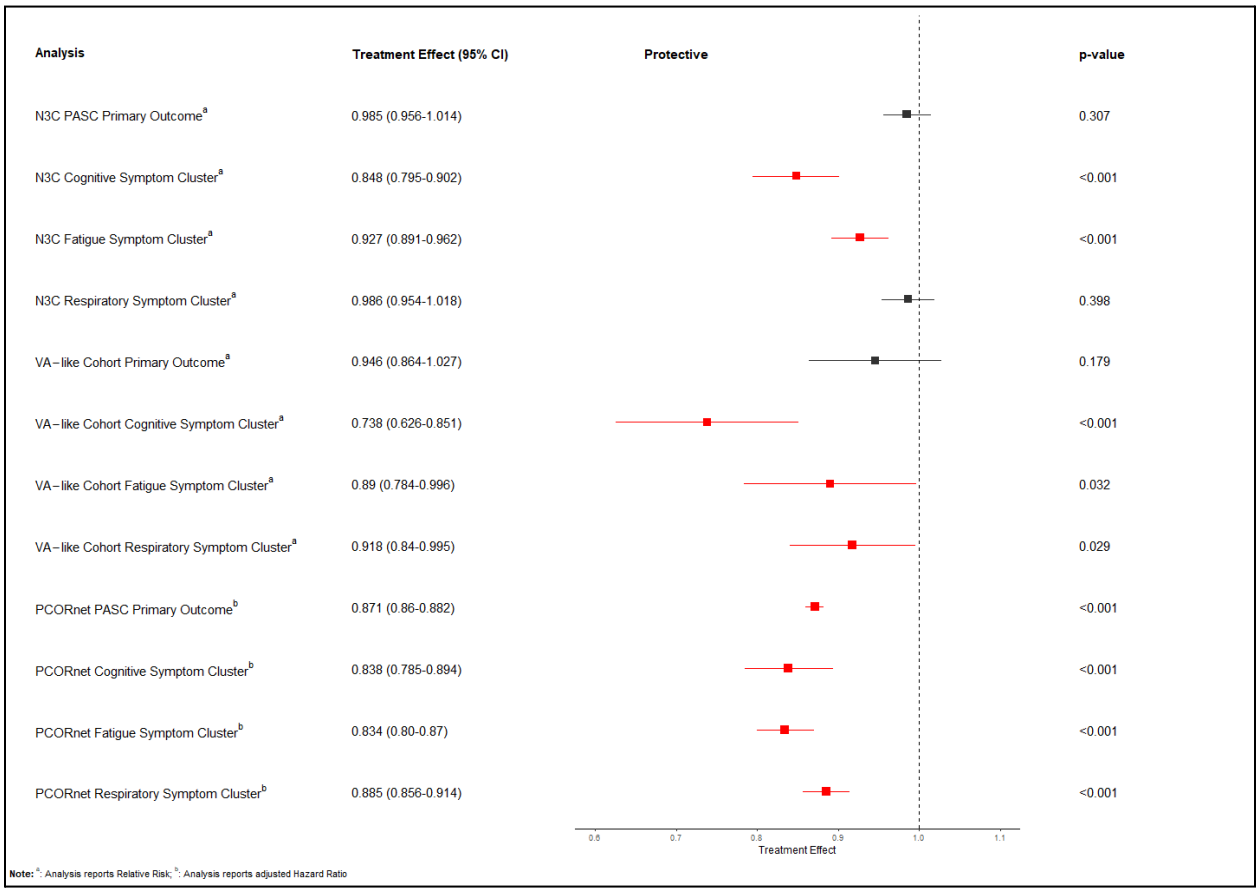
Effect of Paxlovid Treatment on PASC Incidence

Table 2 shows inverse probability of treatment-weighted Aalen-Johansen estimates of cumulative incidence for all main analyses, and Figure 2 shows corresponding risk ratios. Additional figures are shown in Supplement A.

Table 2: Estimated Cumulative Incidence of PASC among Paxlovid-treated patients compared to non-Paxlovid treated patients across all analyses

Analysis	Cumulative Incidence (95% CI)	
	Paxlovid	No Paxlovid
Main Results		
N3C PASC Primary Outcome	0.069 (0.067, 0.071)	0.070 (0.069, 0.071)
N3C Cognitive Symptom Cluster	0.015 (0.014, 0.015)	0.017 (0.017, 0.018)
N3C Fatigue Symptom Cluster	0.040 (0.039, 0.041)	0.043 (0.042, 0.044)
N3C Respiratory Symptom Cluster	0.069 (0.067, 0.071)	0.070 (0.068, 0.071)
Validation Analysis		
VA-like Cohort Primary Outcome	0.078 (0.072, 0.084)	0.082 (0.079, 0.085)
VA-like Cohort Cognitive Symptom Cluster	0.021 (0.018, 0.024)	0.028 (0.027, 0.030)
VA-like Cohort Fatigue Symptom Cluster	0.049 (0.044, 0.054)	0.055 (0.053, 0.057)
VA-like Cohort Respiratory Symptom Cluster	0.078 (0.072, 0.084)	0.085 (0.083, 0.088)
PCORnet PASC Primary Outcome	0.310 (0.308, 0.313)	0.344 (0.342, 0.346)
PCORnet Cognitive Symptom Cluster	0.013 (0.012, 0.013)	0.015 (0.014, 0.016)
PCORnet Fatigue Symptom Cluster	0.036 (0.035, 0.038)	0.043 (0.042, 0.044)
PCORnet Respiratory Symptom Cluster	0.069 (0.068, 0.071)	0.078 (0.076, 0.079)

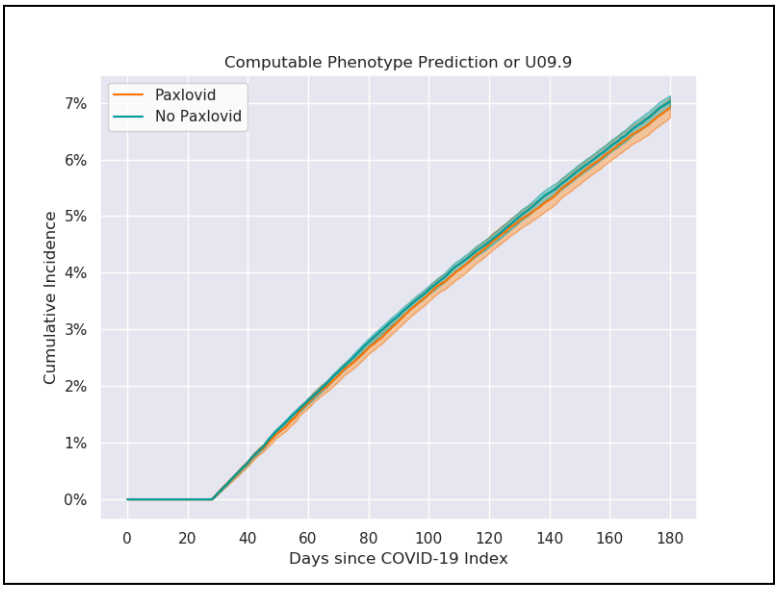
Figure 2: Estimated Treatment Effects of Paxlovid on PASC, across all analyses



Primary Outcome (PASC Computable Phenotype or U09.9 Diagnosis)

Adjusted cumulative incidence estimates were 6.92% (95% CI 6.74-7.09) for treated patients and 7.02% (95% CI 6.91-7.13) for untreated patients (See Figure 3). The adjusted relative risk of PASC was 0.99 (95% CI 0.96-1.01).

Figure 3: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with threshold of 0.9 or U09.9; between 29-180 days



Secondary Outcomes (GBD Symptom Clusters)

Adjusted relative risk was 0.85 (95% CI 0.79-0.90) for the cognitive symptom cluster, 0.93 (95% CI 0.89-0.96) for the fatigue symptom cluster, and 0.99 (95% CI 0.95-1.02) for the respiratory symptom cluster.

Subanalyses

In the "VA-like cohort" subanalysis, the cohort included 61,604 male patients 65 years or older with a COVID-19 index between January 3, 2022, and December 31, 2022 (the same study period used in Xie et al, 2023).[17] Of this cohort, 15,846 (25.72%) were treated with Paxlovid. Adjusted relative risk for the primary outcome was 0.95 (95% CI 0.86-1.03). For the cognitive, fatigue, and respiratory GBD symptom clusters, adjusted relative risk was 0.74 (95% CI

0.63-0.85), 0.89 (95% CI 0.78-0.99), and 0.92 (95% CI 0.84-0.99), respectively. Figures are shown in Supplement B.

In the PCORnet subanalysis, the cohort included 490,487 patients, 35.67% of whom were treated with Paxlovid. The adjusted hazard ratio of Paxlovid treatment on the primary outcome (based on the novel onset of any of 25 symptoms) was 0.87 (95% CI 0.86-0.88). The adjusted hazard ratio of Paxlovid treatment on the GBD symptom clusters was 0.84 (95% CI 0.79-0.89) for cognitive, 0.83 (95% CI 0.80-0.87) for fatigue, and 0.89 (95% CI 0.86-0.91) for respiratory symptoms. See Supplement C for details.

DISCUSSION

In this target trial emulation using the N3C database, we found no significant difference in the cumulative incidence of PASC between individuals treated and untreated with Paxlovid during the acute phase of COVID-19.

We found that Paxlovid had a protective effect against the onset of novel cognitive and fatigue symptoms in the post-acute period, which suggests that Paxlovid may have more impact on the underlying causes of those symptoms. In the literature, multiple PASC etiologies have been proposed. The chief hypotheses are that, relative to healthy convalescents, those with PASC may be experiencing (1) an aberrant autoimmune response triggered by the virus, (2) organ, tissue, or vascular dysfunction related to inflammatory cascades following infection, and/or (3) persistent viremia due to increased viral load or viral reservoirs. We do not yet know which symptoms are caused by which mechanisms. Paxlovid treatment decreases viral load, and thus could plausibly have more impact on symptoms arising from the third factor.[25] Our findings allow us to generate the hypothesis that cognitive symptoms (against which Paxlovid is most protective) may be caused by mechanisms that Paxlovid would affect (e.g., viral load).

Subanalyses

The PCORnet subanalysis differed from our primary analysis in two ways: a different data repository and a broader primary definition of PASC. Whereas we found no significant treatment effect in the primary analysis, the PCORnet subanalysis found that Paxlovid treatment reduced PASC incidence by 13%. Given the broader definition, the unadjusted prevalence of PASC in the PCORnet cohort was also much higher (23.2% vs 5.7%). Unadjusted relative risk also differed across the cohorts. For the cognitive and fatigue GBD symptom clusters, relative risks were similar, while the PCORnet subanalysis found a stronger effect for the respiratory cluster. In sum, the PCORnet subanalysis affirms that the effect of Paxlovid on reducing risk of PASC may not be as high as previously reported, but also demonstrates how cohort differences and varied PASC definitions can affect conclusions.

The “VA-like” subanalysis, limited to a cohort of males at least 65 years old, found a much smaller treatment effect than Xie et al. (2023).[17] Despite our efforts to align outcome measures, cohort characteristics, and methodology, significant differences remain between our subanalysis and the VA study. Chief among them are remaining differences in our cohort and a true VA

cohort. Veterans are more likely than demographically similar non-veterans to have been exposed to traumatic brain injury, post-traumatic stress disorder, biohazards, and other risk factors.[26–30] Through consistent access to the VA, the EHR for veterans may also be more complete.[31] Veterans may also differ from demographically similar non-veterans in their access to care. These factors may account for the large difference in PASC incidence and unadjusted and adjusted relative risk between our subanalysis and Xie et al. (2023).[17]

Implications of Findings

Although our study did not find that Paxlovid has a practically or statistically significant effect in preventing PASC, it should not obscure the body of evidence that it is effective in preventing hospitalization and death due to acute COVID-19.[3,4,32,33] Ultimately, effective treatment and prevention of PASC remains elusive. The RECOVER-VITAL trial will provide strong evidence on whether Paxlovid is safe and effective in treating PASC.[34] However, in addition to studying its potential role as a PASC treatment, there is also a need for trials to explore Paxlovid's potential as a preventative measure for PASC. The target trial emulation framework employed here allows us to draw initial conclusions while we lack results from a randomized controlled trial. Notably, our results contrast with recent media coverage of Paxlovid's effect on PASC, with NBC News reporting in October 2023 that "A consensus has emerged among experts who study and treat long Covid: Paxlovid seems to reduce the risk of lingering symptoms among those eligible to take it."[35] Our findings bring this interpretation into question.

Strengths and Limitations

This study has several strengths that underscore the value of large-scale EHR repositories. We used a large, nationally sampled cohort from 28 sites across the United States, increasing generalizability and decreasing the potential for misclassification present in administrative or claims data.[36] The volume of data in the N3C database allowed for the aggressive inclusion/exclusion criteria necessary for TTE while preserving statistical power.[37,38] Our use of the TTE framework allowed us to account for confounding and estimate the causal effect of Paxlovid treatment using observational data.[39–42]

Our use of a PASC computable phenotype is also a strength. Although several institutions have proposed definitions of PASC, they disagree on the symptoms and timing that constitute the condition.[43–46] Varying definitions of PASC can lead to widely varying incidence estimates.

Furthermore, measuring PASC as the novel onset of a specific set of symptoms can lead to false positives (symptoms with etiologies other than COVID-19) and false negatives (related symptoms not included in the definition). A machine learning-based computable phenotype may learn to avoid these errors. Furthermore, it does not require the selection of a principled set of symptoms, instead learning from all symptoms associated with PASC diagnoses.

Our study period makes our findings more relevant. Prior studies of this topic have included cases from the initial Omicron wave, when Paxlovid was less available and disease dynamics were markedly different. Finally, our subanalyses shed further light on potential demographic and cohort effects.

This study also has limitations. Because EHR data do not include information on adherence, we can only measure whether a patient was prescribed Paxlovid. However, this is adequate for estimating the intention-to-treat effect. Also, our inclusion criteria of Paxlovid treatment within five days of COVID-19 index differs from the indication of treatment within five days of symptom onset. However, we note that within our cohort, 96% of treated patients were treated within one day of COVID-19 index.

Several variables in this study are subject to measurement error. Many COVID-19 infections during this period were not documented due to the prevalence of home testing. Paxlovid prescriptions from providers outside N3C data partner systems may not be documented. The PASC computable phenotype may also misclassify patients.[47] For this reason, the confidence intervals around computable phenotype-based incidence estimates are likely too narrow.

Finally, this study is subject to limitations common to EHR-based studies and causal inference studies. EHRs are susceptible to missing data, and our estimates may be biased if missingness was related to unobserved confounding.[48–50] This study is also subject to the assumptions of all causal inference studies, in particular, that there is no unmeasured confounding.

Conclusion

There is overwhelming evidence that Paxlovid is effective in preventing hospitalization and death due to acute COVID-19, and as such is a critical treatment option to improve COVID-19 outcomes. We used a target trial emulation framework to determine whether Paxlovid might also be effective in preventing PASC. Among patients with COVID-19 in our study period who were

eligible for Paxlovid treatment, the cumulative incidence of PASC within a 180-day follow-up period was not significantly lower in patients treated with Paxlovid. Based on these findings, we do not see evidence of Paxlovid's effectiveness as a preventative against PASC in general. However, we also find evidence that the treatment effect varies by symptom type and patient population. Future research will explore potential heterogeneous treatment effects across PASC subphenotypes and demographic groups.

METHODS

This study is part of the NIH Researching COVID to Enhance Recover (RECOVER) Initiative, which seeks to understand, treat, and prevent PASC. For more information on RECOVER, visit https://recovercovid.org. All analyses described here were performed within the secure N3C Data Enclave.

We emulated a target trial to estimate the effect of Paxlovid treatment during acute COVID-19 on the cumulative incidence of PASC. We followed a two-step process for emulating target trials with observational data: first, we articulated the causal question of interest in the form of a hypothetical trial protocol (Table 3).[51] Second, we emulated each component of this protocol using the N3C Enclave, which integrates EHR data for 21 million patients from 83 data partners across the United States. N3C's methods for data acquisition, ingestion, and harmonization have been reported elsewhere.[20,52,53] All results are reported in adherence with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[54]

Table 3: Protocol of a Target Trial Emulation to Estimate the Effect of Paxlovid Treatment during Acute COVID-19 on Cumulative PASC Incidence

Protocol Component	Description under Target Trial Conditions	Method of Target Trial Emulation
Eligibility criteria	Persons aged 18 and older who have an acute COVID-19 infection and one or more risk factors for severe COVID-19 as per CDC guidelines.[55]	Persons aged 18 and older who have one or more risk factors for severe COVID-19 as per CDC guidelines[55] and who have had a COVID-19 index (either a documented COVID-19 diagnosis or positive SARS-CoV-2 lab test) during the study period.
Treatment strategies	Complete course of Paxlovid initiated within 5 days of symptom onset.	Complete course of Paxlovid prescribed within 5 days of COVID-19 index.
Assignment procedures	Participants will be randomly assigned to treatment or control at baseline and will be aware of their treatment assignment.	Patients will be assigned weights based on treatment propensity scores to ensure exchangeability of treatment and control groups and emulate random assignment.
Follow-up period	Each patient will be followed for 180 days after treatment.	Patients will be censored at 180 days after COVID-19 index or the time of their last recorded visit, whichever is earlier.
Outcome	Clinical diagnosis of PASC within follow-up period	Clinical diagnosis of PASC or computed probability of PASC > 0.9 between 29 and 180 days after COVID-19 index. Patients with a PASC diagnosis or prediction within 28 days of COVID-19 index will be censored.
Causal contrasts	Intention-to-treat effect	Intention-to-treat effect
Analysis plan	Measure relative risk of PASC diagnosis across treatment arms.	Estimate cumulative incidence of PASC in each treatment arm using Aalen-Johansen estimators weighted for treatment propensity; estimate relative risk based on point estimates and variances of cumulative incidence estimates.

Eligibility Criteria

The study period spanned April 1, 2022, to August 31, 2023, with an index cutoff date of February 28, 2023 (180 days before the end of the study period). We excluded the period between December 21, 2021 (date of Paxlovid EUA) and March 31, 2022 due to the variability in case counts and prescription patterns during the first wave of the Omicron variant.[56] We used data from RECOVER release v141 (August 14, 2023) in the N3C Enclave.

Our inclusion criteria emulated the target trial's eligibility criteria: 1) having a documented COVID-19 index date within the study period (with *index date* defined as the earliest date of either a COVID-19 diagnosis [ICD-10 code U07.1] or a positive SARS-CoV-2 test result), 2) being ≥ 18 years of age at the COVID-19 index date (due to potential differences in clinical characteristics and prescription practices between pediatric and adult patients[57,58]), and 3) having ≥ 1 risk factor for severe COVID-19 per CDC guidelines (age ≥ 50 years or diagnosis of a comorbidity associated with higher risk of severe COVID-19[55]). For patients with > 1 COVID-19 index date in the study period, we selected a single index date per the following criteria: 1) if Paxlovid was prescribed within 5 days of one index date, use that index date, 2) if Paxlovid was prescribed within 5 days of > 1 index date, use the first, and 3) if Paxlovid was not prescribed within 5 days of any index date, use the first index date.

We also applied a set of exclusion criteria, to exclude: 1) patients who were hospitalized on the COVID-19 index date, 2) patients with PASC (see Treatment and Outcome) prior to or on the COVID-19 index date, 3) patients who were prescribed a drug with a severe interaction with Paxlovid in the 30 days prior to the COVID-19 index.[59] Furthermore, to ensure that data were captured from sites with high fidelity and adequate coverage, we only included data from 28 sites with at least 5% of eligible patients, and a minimum of 500 patients, treated with Paxlovid during the study period.

Treatment and Outcome

Eligible patients were categorized by their treatment exposure. The treatment group was defined as having been prescribed Paxlovid within 5 days of their COVID-19 index date. The control group was defined as the complement, with one exception. Patients who were prescribed Paxlovid within 5 days of COVID-19 index, but were hospitalized prior to treatment, were included in the control group and censored at the date of Paxlovid prescription (see Statistical

Analysis for more on censoring). We took this approach because inpatient Paxlovid treatment (presumably after COVID-19 is already severe) is a different treatment modality, and we intended to study on-label outpatient treatment. We selected a treatment window of 5 days from COVID-19 index to adhere as closely as possible to treatment guidelines (within 5 days of symptom onset) with the available data. We identified 10 Observational Medical Outcomes Partnership [OMOP] concepts that correspond to Paxlovid in N3C and used these concepts to measure treatment.[60]

We considered two measures of the PASC outcome. Our primary outcome leveraged a computable phenotype: a machine learning model trained to predict PASC diagnoses (ICD-10 code U09.9). An earlier version of this computable phenotype was used in prior work. For this study, we used an updated version better suited for the later phase of the pandemic.[22,61] We followed patients for 180 days following their COVID-19 index date. PASC date was defined as the date of the maximum computable phenotype prediction above a threshold of 0.9, or, if present, the date of U09.9 diagnosis, whichever was earlier. Computable phenotype model scores were not generated for patients. Patients over 100 years old at COVID-19 index did not receive model scores and were excluded from the primary outcome analysis.

Our secondary outcome examined PASC symptom clusters--cognitive, fatigue, and respiratory--proposed by the Global Burden of Disease (GBD) program ("GBD symptom clusters" henceforth).[23] For the GBD symptom cluster outcomes, PASC date was defined as the onset date of any novel symptom in the cluster at least 28 days after COVID-19 index (we defined novel symptoms as symptoms that did not occur in the three years prior to COVID-19 index).

Statistical Analysis

Our estimand was the cumulative incidence of PASC from 29 to 180 days after COVID-19 index. We applied a potential outcomes framework to compare the rate of PASC among patients who received treatment to those who did not. We use inverse probability of treatment (IPT) weighting to emulate random assignment through exchangeability between treatment arms. Our treatment model included the following pre-treatment covariates: sex, age (binned), race and ethnicity, Charlson Comorbidity Index (CCI; binned), Community Well-Being Index (CWBI; binned), number of visits in the year prior to index (binned), number of hospitalizations in the year prior to index (binned), month of COVID-19 onset, and site of care provision. Our rationale

for using these covariates is as follows. Many studies have shown disparity in COVID-19 treatment and outcome by race, ethnicity, and social determinants of health.[62–65] Sex, age, and comorbidities are known to affect care seeking and the outcome of COVID-19. Past healthcare utilization could affect the likelihood of treatment seeking and PASC documentation. Finally, the index month was included because Paxlovid treatment rates, viral variants, and infection rates changed during the study period. CCI was coded as missing when no condition records were present in N3C prior to index. CWBI was coded as missing when patient ZIP code was not reported. We used this treatment model to generate stabilized IPT weights trimmed at the 99.5th percentile. We assessed covariate balance using absolute standardized differences. To estimate the cumulative incidence of PASC, we used IPT-weighted Aalen-Johansen estimators. We used bootstrapping with 200 iterations to estimate the 95% confidence interval at an alpha of 0.05.

We censored patients at the following events: 1) death, 2) last documented visit in the study period, 3) PASC outcome within 28 days of COVID-19 index, and 4) 180 days after index (end of study period). We also censored patients in the control group if they received Paxlovid. This could occur if they received Paxlovid within 5 days of index, but after hospitalization (see Treatment and Outcome). It could also occur if they received Paxlovid later in the study period, but not within 5 days of a COVID-19 index (see Eligibility Criteria).

In addition, we conducted two supplementary analyses (Supplements D and E) and five sensitivity analyses (Supplement F).

Subanalyses

To validate our results against both the current state of literature, and against other observational patient-level datasets, we conduct two subanalyses. The first attempted to mirror the cohort used in Xie et al (2023). We refer to this as the “VA-like cohort”. In this analysis , we used the same study start and end dates as Xie et al. (January 3, 2022, and December 31, 2022). To mirror VA demographics, we filtered the cohort to males >= 65 years old at COVID-19 index. To reflect the high continuity of care of the VA system, we filtered our cohort to patients with at least two visits in the year prior to COVID-19 index.

Additionally, we collaborated with colleagues from the PCORnet Clinical Research Network’s RECOVER EHR cohort to run a similar analysis across records from 29 sites. This analysis used PCORnet’s rules-based PASC definition, which is based on the novel onset of any of 25

symptoms, as the primary outcome.[66,67] Detailed methods and results for this analysis are shown in Supplement C.

DISCLOSURES

This group of authors has no relevant disclosures to report.

AUTHOR CONTRIBUTIONS

Authorship has been determined according to ICMJE recommendations.

DATA SHARING

The N3C data transfer to NCATS is performed under a Johns Hopkins University reliance protocol (IRB00249128) or individual site agreements with the NIH. The N3C Data Enclave is managed under the authority of the NIH; more information can be found at ncats.nih.gov/n3c/resources. Enclave data is protected, and can be accessed for COVID-19-related research with an institutional review board-approved protocol and data use request. The Data Use Request ID for this study is RP-5677B5. Enclave and data access instructions can be found at https://covid.cd2h.org/for-researchers. All code used to produce the analyses in this manuscript is available within the N3C Data Enclave to users with valid login credentials to support reproducibility.

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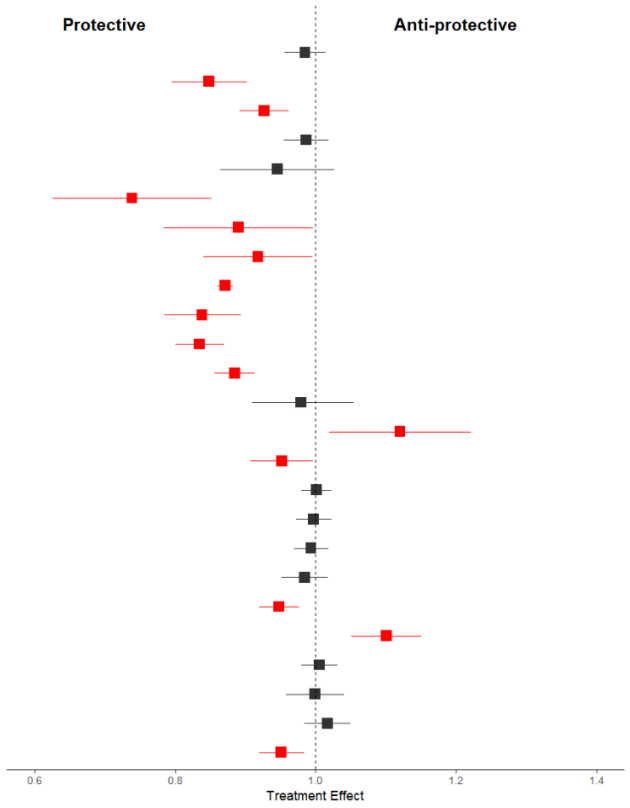
SUPPLEMENT A - ADDITIONAL TABLES AND FIGURES

Table SA1- Estimated treatment effects across all analyses

Analysis	Cumulative Incidence (95% CI)		Supplement
	Paxlovid	No Paxlovid	
Main Results			
N3C PASC Primary Outcome	0.069 (0.067, 0.071)	0.070 (0.069, 0.071)	A
N3C Cognitive Symptom Cluster	0.015 (0.014, 0.015)	0.017 (0.017, 0.018)	A
N3C Fatigue Symptom Cluster	0.040 (0.039, 0.041)	0.043 (0.042, 0.044)	A
N3C Respiratory Symptom Cluster	0.069 (0.067, 0.071)	0.070 (0.068, 0.071)	A
Validation Analysis			
VA-like Cohort Primary Outcome	0.078 (0.072, 0.084)	0.082 (0.079, 0.085)	B
VA-like Cohort Cognitive Symptom Cluster	0.021 (0.018, 0.024)	0.028 (0.027, 0.030)	B
VA-like Cohort Fatigue Symptom Cluster	0.049 (0.044, 0.054)	0.055 (0.053, 0.057)	B
VA-like Cohort Respiratory Symptom Cluster	0.078 (0.072, 0.084)	0.085 (0.083, 0.088)	B
PCORnet PASC Primary Outcome	0.310 (0.308, 0.313)	0.344 (0.342, 0.346)	C
PCORnet Cognitive Symptom Cluster	0.013 (0.012, 0.013)	0.015 (0.014, 0.016)	C
PCORnet Fatigue Symptom Cluster	0.036 (0.035, 0.038)	0.043 (0.042, 0.044)	C
PCORnet Respiratory Symptom Cluster	0.069 (0.068, 0.071)	0.078 (0.076, 0.079)	C
PCORnet U09.9 Diagnosis	0.085 (0.078, 0.092)	0.092 (0.089, 0.095)	C
Supplementary Analysis			
N3C U09.9 Code Diagnosis	0.008 (0.007, 0.008)	0.007 (0.006, 0.007)	D
N3C PASC Primary Outcome, Vaccination-Aware	0.061 (0.058, 0.063)	0.064 (0.062, 0.065)	E
Sensitivity Analysis			
N3C PASC Computable Phenotype Threshold - 0.75	0.137 (0.135, 0.140)	0.137 (0.136, 0.139)	F
N3C PASC Computable Phenotype Threshold - 0.80	0.114 (0.112, 0.117)	0.115 (0.113, 0.116)	F
N3C PASC Computable Phenotype Threshold - 0.85	0.092 (0.090, 0.094)	0.093 (0.092, 0.094)	F
N3C PASC Computable Phenotype Threshold - 0.95	0.047 (0.046, 0.049)	0.048 (0.047, 0.049)	F
N3C Paxlovid Treatment as Index Event	0.069 (0.067, 0.070)	0.071 (0.070, 0.072)	F
N3C Positive Lab-only Index Events	0.074 (0.071, 0.077)	0.067 (0.066, 0.068)	F
N3C PASC Primary Outcome (29-365 days)	0.127 (0.124, 0.130)	0.126 (0.125, 0.128)	F
N3C PASC Primary Outcome(90-180 days)	0.039 (0.038, 0.041)	0.040 (0.039, 0.040)	F
N3C PASC Primary Outcome (90-365 days)	0.099 (0.096, 0.102)	0.098 (0.096, 0.099)	F
N3C Doubly Robust Adjustment	Hazard Ratio: 0.951 (0.920, 0.984)		F

Figure SA1- Forest Plot of Treatment Effects across all analyses

Analysis	Treatment Effect (95% CI)	p-value
N3C PASC Primary Outcome[a]	0.985 (0.956-1.014)	0.307
N3C Cognitive Symptom Cluster[a]	0.848 (0.795-0.902)	<0.001
N3C Fatigue Symptom Cluster[a]	0.927 (0.891-0.962)	<0.001
N3C Respiratory Symptom Cluster[a]	0.986 (0.954-1.018)	0.398
VA – like Cohort Primary Outcome[a]	0.946 (0.864-1.027)	0.179
VA – like Cohort Cognitive Symptom Cluster[a]	0.738 (0.626-0.851)	<0.001
VA – like Cohort Fatigue Symptom Cluster[a]	0.89 (0.784-0.996)	0.032
VA – like Cohort Respiratory Symptom Cluster[a]	0.918 (0.84-0.995)	0.029
PCORnet PASC Primary Outcome[b]	0.871 (0.86-0.882)	<0.001
PCORnet Cognitive Symptom Cluster[b]	0.838 (0.785-0.894)	<0.001
PCORnet Fatigue Symptom Cluster[b]	0.834 (0.80-0.87)	<0.001
PCORnet Respiratory Symptom Cluster[b]	0.885 (0.856-0.914)	<0.001
PCORnet Incident U09.9 / B94.8 Code[b]	0.979 (0.909-1.054)	0.573
N3C Incident U09.9 Code[a]	1.12 (1.02-1.22)	0.027
N3C Vaccination – Aware results[a]	0.952 (0.907-0.997)	0.031
N3C PASC Computable Phenotype Threshold – 0.75[a]	1.001 (0.979-1.022)	0.943
N3C PASC Computable Phenotype Threshold – 0.8[a]	0.997 (0.972-1.022)	0.829
N3C PASC Computable Phenotype Threshold – 0.85[a]	0.993 (0.969-1.018)	0.592
N3C PASC Computable Phenotype Threshold – 0.95[a]	0.984 (0.951-1.017)	0.351
N3C Paxlovid Treatment as index event[a]	0.948 (0.92-0.976)	<0.001
N3C Positive lab – only index events[a]	1.101 (1.051-1.15)	<0.001
N3C PASC Primary Outcome (29 – 365 days)[a]	1.005 (0.98-1.031)	0.698
N3C PASC Primary Outcome(90 – 180 days)[a]	0.999 (0.957-1.04)	0.95
N3C PASC Primary Outcome (90 – 365 days)[a]	1.017 (0.984-1.049)	0.317
N3C Doubly Robust Adjustment[b]	0.951 (0.92-0.984)	0.003



Note: [a]: Analysis reports Relative Risk; [b]: Analysis reports adjusted Hazard Ratio

Figure SA2- Covariate Balance (N3C Cohort)

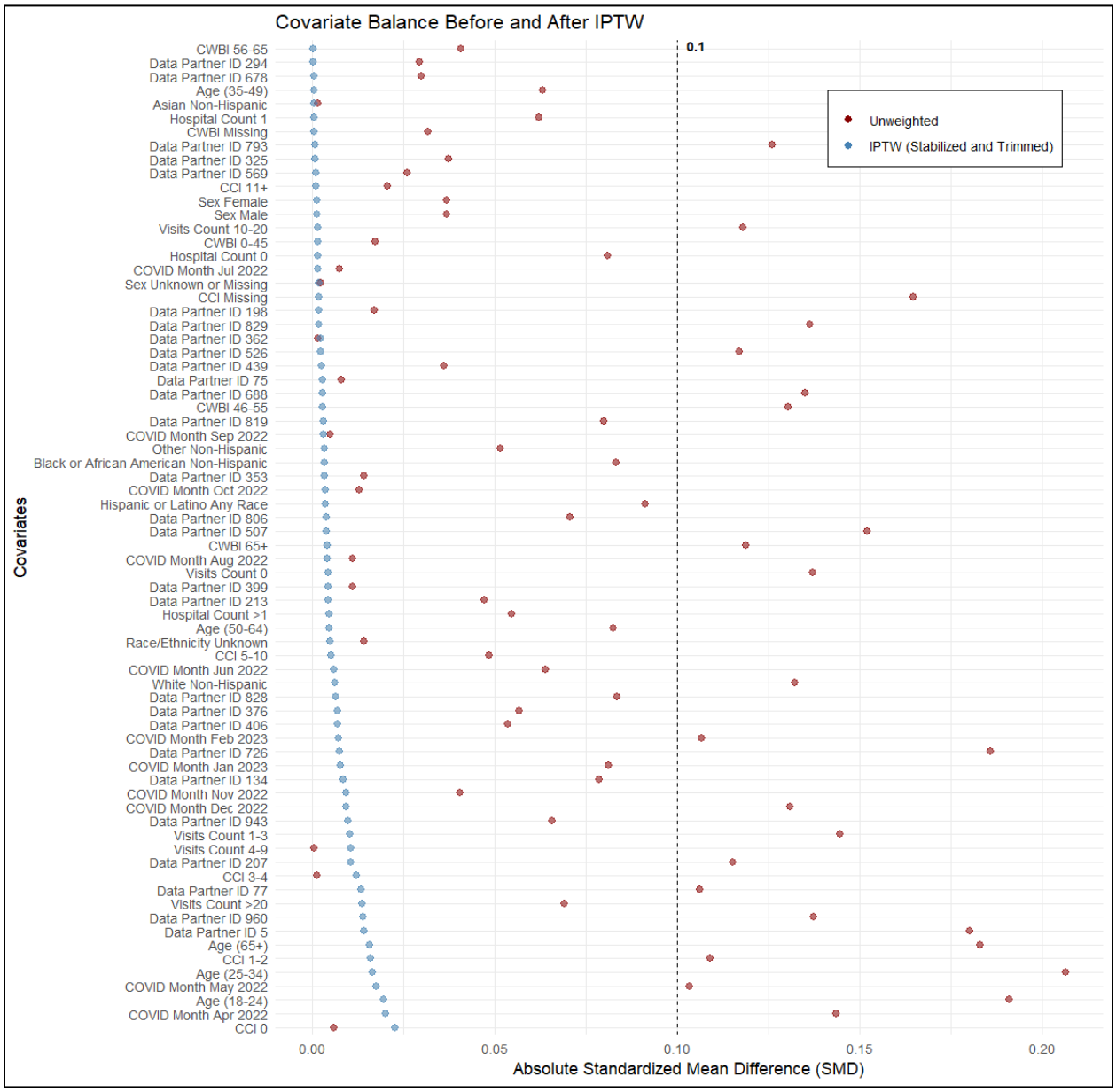
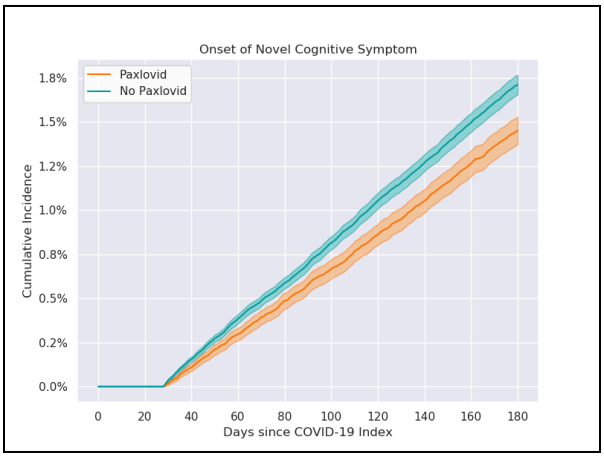
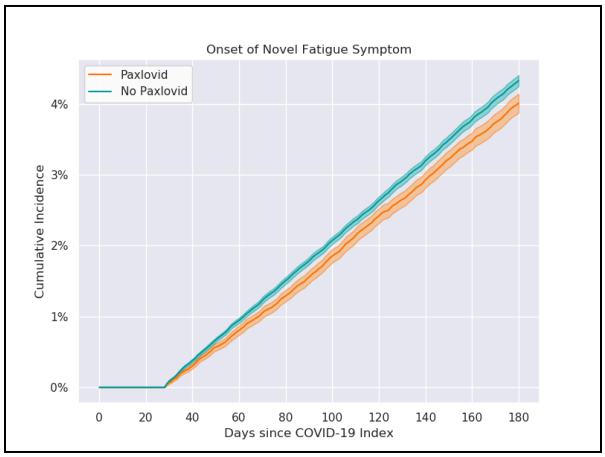
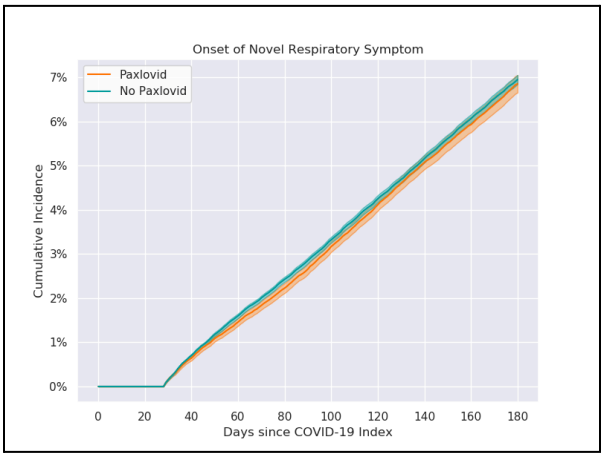


Figure SA3: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by GBD Symptom Clusters







SUPPLEMENT B - ADDITIONAL FIGURES, VA-LIKE SUBANALYSIS

Figure SB1: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with threshold of 0.9 or U09.9, VA-like Subanalysis

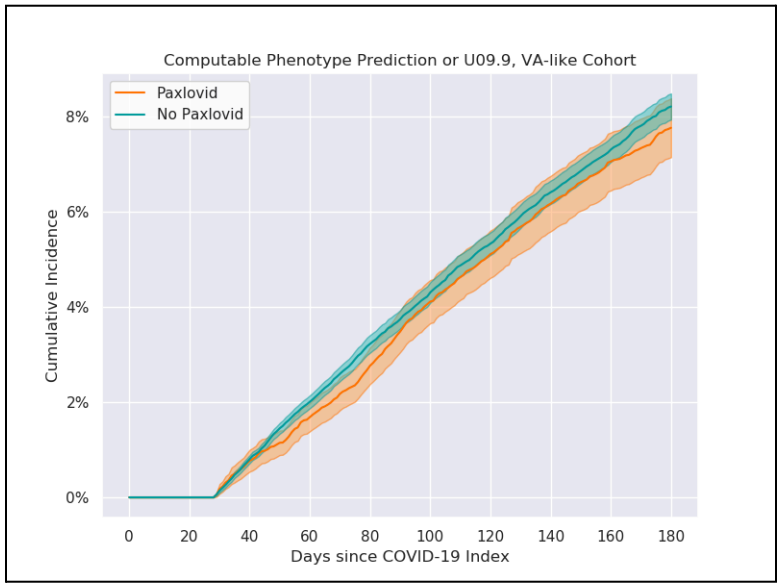
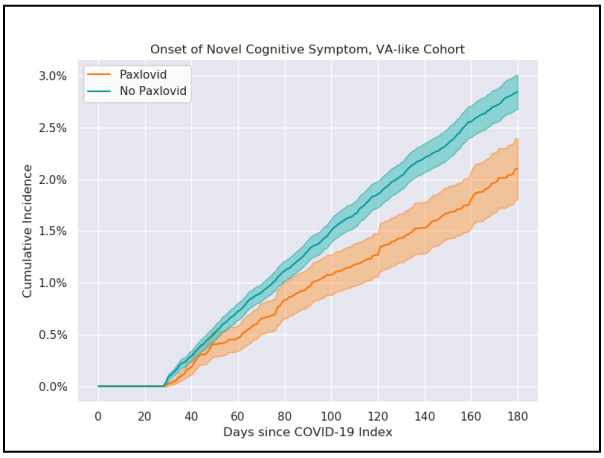
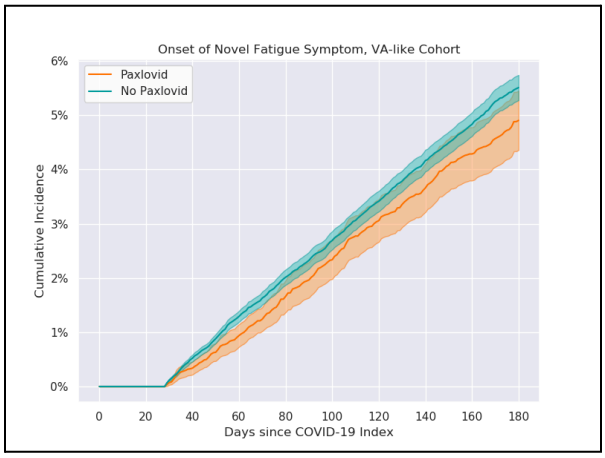
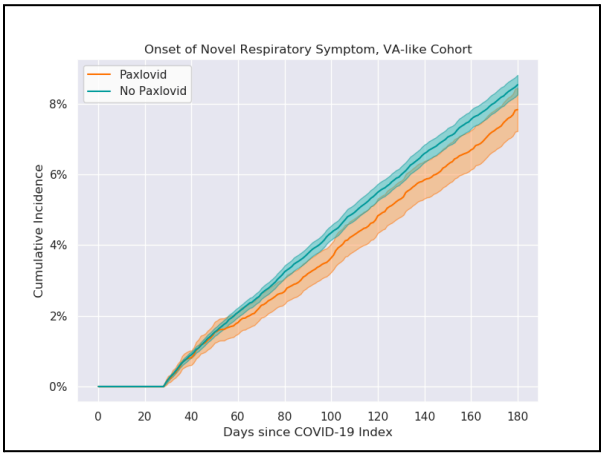


Figure SB2: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by GBD Symptom Clusters, VA-like Subanalysis







SUPPLEMENT C - PCORNET SUBANALYSIS

Methods

The PCORnet's Long COVID definition for adult is rules-based by leveraging ICD codes covering 25 clinical symptoms, including anemia, thromboembolism, pulmonary embolism, dementia, pulmonary fibrosis/edema/inflammation, smell and taste, diabetes mellitus, malnutrition, fluid disorders, general PASC diagnoses U099/B948, encephalopathy, abnormal heartbeat, chest pain, abdominal pain, constipation, joint pain, cognitive problems, headache, sleep wake disorders, dyspnea (or shortness of breath), acute pharyngitis, hair loss, edema, fever, malaise and fatigue.[66,67] The incident post-acute sequelae of SARS-CoV-2 (PASC) symptoms from the list above was observed during the post-acute phase (30 to 180 days after the index date), while absent during the baseline period (7 days to 3 years preceding the index date). Individuals classified as having incident PASC when he/she exhibited at least one incident PASC-related symptom during the post-acute phase.

The same set of covariates as N3C were built for the adjustment analyses, including age, self-reported sex, race/ethnicity, CCI score, baseline hospitalization utilization, social-economic status and infection time. The social-economic status was quantified by the national-level area deprivation index (ADI) linked by either 9-digit zip code or geocode. The IPTW re-weighted survival analyses, including Cox proportional hazard model for the relative risk, and the Aalen-Johansen model for the cumulative incidence. Both methods considered the death to be a competing risk for the target incident outcomes. The IPTW weights were learned based on method from Zang et al.[68]

Results

Table SC1: Estimated treatment effects across all analyses, PCORnet Subanalysis

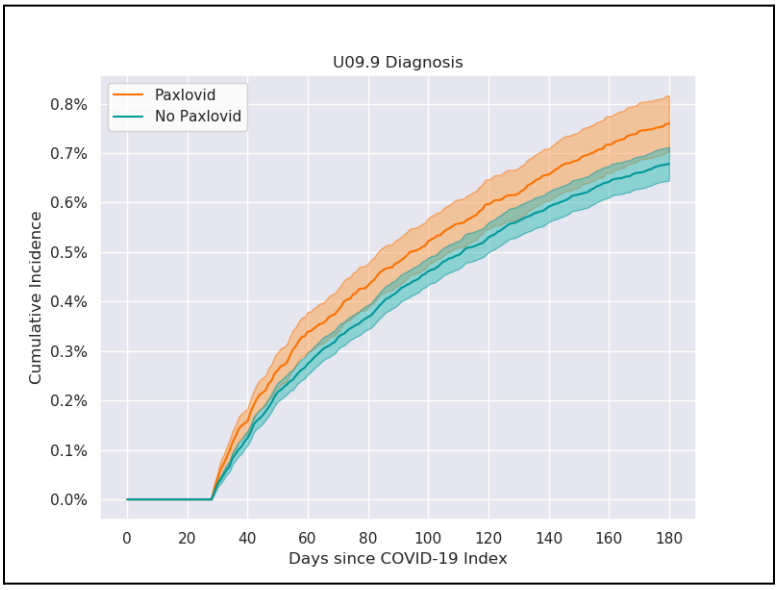
PCORnet Results	Adjusted Aalen-Johansen Cumulative Incidence Estimate (95% CI)		Adjusted Hazard Ratio (95% CI)	p-value (Welch's t test, two-sample, two-sided)
	Paxlovid	No Paxlovid		
Incident PASC	0.310 (0.308, 0.313)	0.344 (0.342, 0.346)	0.871 (0.860, 0.882)	<0.001
Incident U099/B948	0.009 (0.008, 0.009)	0.009 (0.009, 0.009)	0.979 (0.909, 1.054)	0.573
Incident GBD Cluster - Cognitive	0.013 (0.012, 0.013)	0.015 (0.014, 0.016)	0.838 (0.785, 0.894)	<0.001
Incident GBD Cluster - Fatigue	0.036 (0.035, 0.038)	0.043 (0.042, 0.044)	0.834 (0.800, 0.870)	<0.001
Incident GBD Cluster - Respiratory	0.069 (0.068, 0.071)	0.078 (0.076, 0.079)	0.885 (0.856, 0.914)	<0.001

SUPPLEMENT D - OUTCOME DEFINED BY CLINICAL DIAGNOSIS

In addition to results from our primary analysis, we defined our outcome of PASC as only patients with a recorded U09.9 diagnoses, indicating a clinician-reported outcome of PASC. For this analysis, we excluded patients from data partners that did not frequently use the U09.9 code. We defined this criterion as at least 1% of patients with a COVID-19 index (across all N3C data, not just in our study period) having a U09.9 diagnosis.

Of the total 426,461 patients, 409,980 (96.14%) remained after applying the site-level U09.9 usage criterion. Without adjustment for covariates, 781 (0.66%) patients treated with Paxlovid had a U09.9 diagnosis in the follow-up period, compared to 1,662 (0.57%) patients in the untreated group. Weighted Aalen-Johansen estimates of cumulative incidence were 0.76% (95% CI 0.70-0.82) for patients treated with Paxlovid and 0.68% (95% CI 0.64-0.71) for patients not treated with Paxlovid. Adjusted relative risk was 1.12 (95% CI 1.02-1.22). (See Figure SD1)

Figure SD1- Cumulative Incidence of PASC in Non-Paxlovid and Paxlovid treated patients, defined by onset of U09.9 diagnosis code

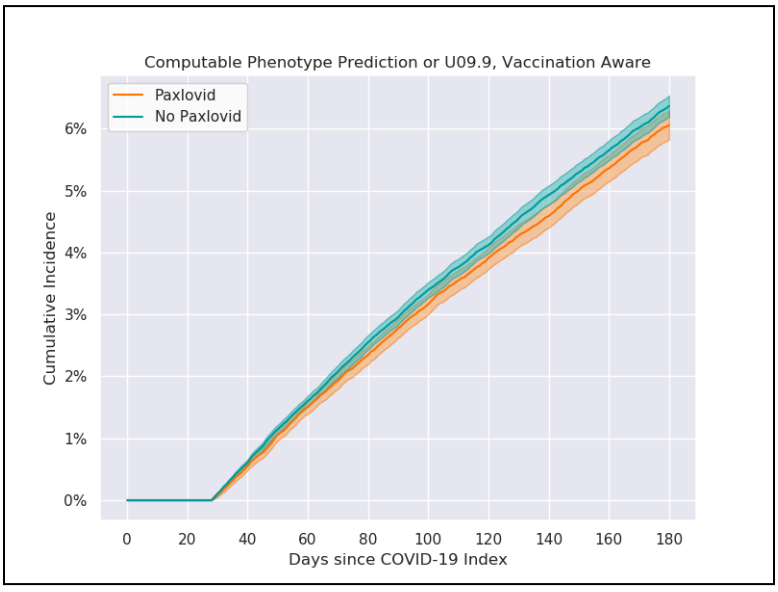


SUPPLEMENT E - VACCINATION-AWARE ANALYSIS

For this supplementary analysis, we included COVID-19 vaccination status as a covariate, and replicated our primary analysis. We considered vaccination to be a plausible confounder of Paxlovid treatment and documented PASC, either through acute infection severity or propensity to seek care. We followed a similar procedure as in our earlier work estimating the effect of Paxlovid treatment on hospitalization.[3] Because vaccination status in N3C is subject to misclassification, we used a subcohort of patients from sites with reliable vaccination data. We categorized patients by their vaccination status prior to their COVID-19 index date, defined as having completed a full course of vaccination at least 14 days prior to index. Partially vaccinated patients and patients who became fully vaccinated fewer than 14 days prior to index were excluded from the analysis.

In the subanalysis including COVID-19 vaccination status as a covariate, the cohort included 164,966 patients from 8 sites that met vaccination data quality criteria. Of this cohort, 59,257 (35.92%) were treated with Paxlovid, and 8,825 (5.35%) had PASC according to our primary outcome measure. Adjusted relative risk was 0.95 (95% CI 0.91-1.00).

Figure SD1 - Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with threshold of 0.9 or U09.9, additionally adjusted for vaccination status and among data partners meeting vaccination data quality criteria



SUPPLEMENT F - SENSITIVITY ANALYSES

Methods

First, we used a doubly-robust estimation method in case the treatment model was misspecified. Targeted maximum likelihood estimation was not feasible with our cohort and computing environment, so we were unable to estimate cumulative incidence using a doubly-robust method. Instead, we estimated the hazard ratio (HR) of Paxlovid treatment as a secondary estimand. We used inverse probability of treatment-weighted Cox proportional hazards models adjusted for the same baseline covariates as the treatment model. The same bootstrap procedure was used to estimate confidence intervals.

Second, we tested various computable phenotype prediction thresholds. In addition to the 0.9 threshold used in the primary analysis, we tested prediction thresholds at 0.75, 0.8, 0.85, and 0.95.

Third, we included Paxlovid treatment as a COVID-19 index event. This added 33,571 additional patients who were treated with Paxlovid during the study period, but did not have a U07.1 diagnosis or a positive lab test in the five days prior to treatment.

Fourth, we also tested sensitivity to COVID-19 index definition by including only positive lab tests as index events (i.e., we did not include U07.1 diagnoses without accompanying lab results).

Fifth, we tested sensitivity to outcome definition in two ways: by requiring outcomes to occur 90 days after COVID-19 index (rather than 29 days) and by observing patients for up to 365 days (rather than 180 days).

Results

Our findings were not sensitive to the use of different computable phenotype prediction thresholds, or to the use of different PASC timing windows.

However, other sensitivity analyses produced different results. Treating only positive lab tests as index events, Paxlovid appeared to have an anti-protective effect on PASC. There is no plausible

mechanism for this to be the case, and it is likely due to bias in the subset of COVID-19 patients who had documented lab tests in an era when home testing was common.

In our analysis including treatment with Paxlovid as a COVID-19 index event (i.e., including patients who received Paxlovid but did not have a COVID-19 diagnosis or positive lab result), we also found a significant, protective treatment effect (RR 0.95, 95% CI 0.92-0.98). In the absence of a COVID-19 diagnostic code (U07.1) or positive laboratory confirmed SARS-CoV-2 test to mark a COVID-19 index date, the additional subset of the patient population treated with Paxlovid here may still represent true COVID-19 cases, treated for suspected (but not laboratory-confirmed COVID-19), or with a recent personal history of COVID-19 (Z86.16).[69] Within the resulting patient cohort, the treatment effect of Paxlovid on PASC was statistically significant, but the effect size remained practically insignificant.

Using a doubly robust estimator and the hazard ratio (HR) of Paxlovid treatment as the estimand, we found a small but significant treatment effect (HR 0.95, 95% CI 0.92-0.98). This suggests that some residual confounding may remain after IPTW, however, the treatment effect remains practically insignificant.

Figure SF1: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with thresholds ranging from 0.75 to 0.95 or U09.9, by CP model threshold

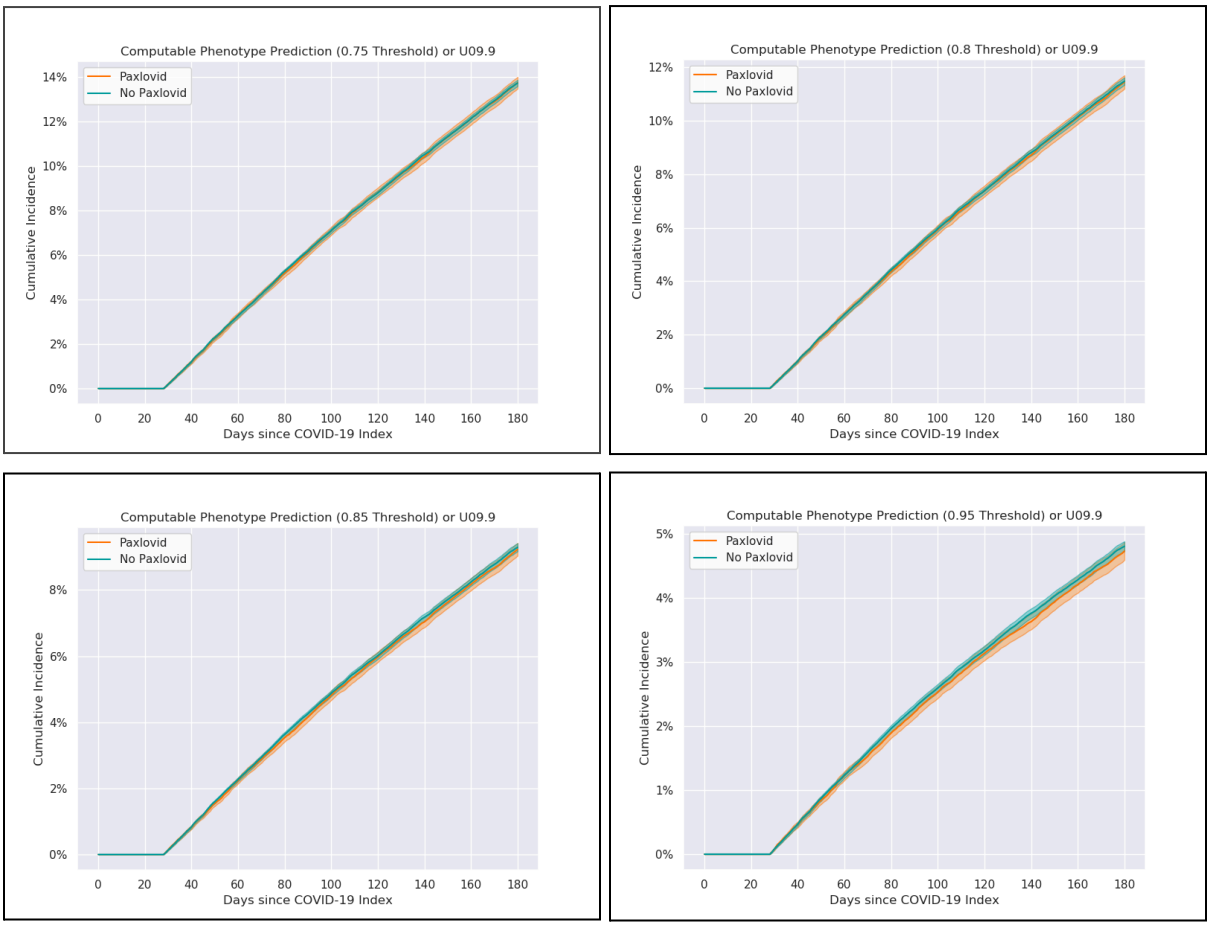


Figure SF2: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with threshold of 0.9 or U09.9, Paxlovid treatments without accompanying lab tests or U07.1 diagnoses included as index events

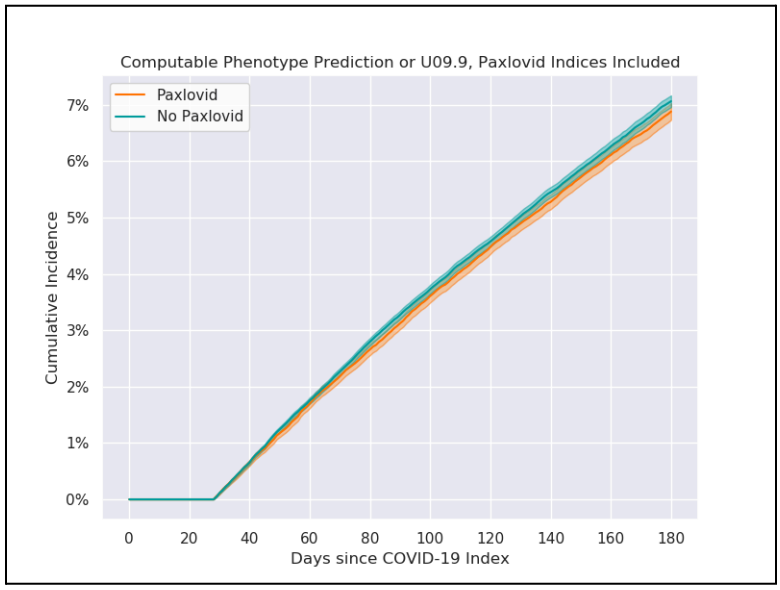


Figure SF3: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with threshold of 0.9 or U09.9, positive lab required for COVID-19 index (i.e., U07.1 diagnoses without accompanying lab tests not included as index events)

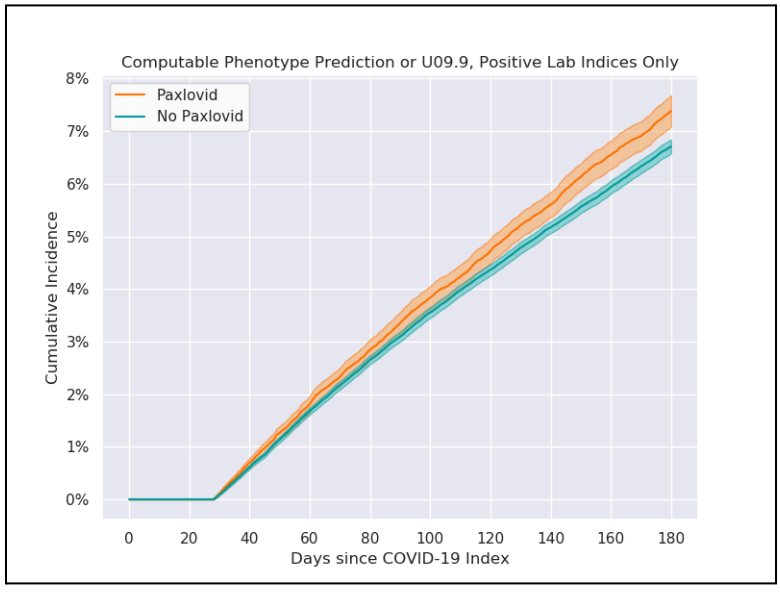


Figure SF4: Cumulative incidence of PASC in Paxlovid treated vs. Non-Paxlovid-Treated patients by predicted outcome from CP model with threshold of 0.9 or U09.9, by time window