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Association of Nirmatrelvir for Acute SARS-CoV-2 Infection with Subsequent Long COVID Symptoms in an Observational Cohort Study

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Author Contributions: Drs. Durstenfeld, Peluso, Henrich, Deeks, and Hsue designed the study with input from the CCS Executive Steering Committee including Drs. Marcus, Beatty, Olgin, Pletcher, and Peyser. Ms. Lin and Dr. Durstenfeld conducted the analyses. Dr. Peyser oversaw data management. Drs. Durstenfeld and Peluso wrote the first draft of the manuscript. Dr. Isasi and Dr. Carton recruited participants and provided critical input on the manuscript. All authors provided critical input and approved of the manuscript.

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Abstract

Background: Oral nirmatrelvir/ritonavir is approved as treatment for acute COVID-19, but the effect of treatment during acute infection on risk of Long COVID is unknown. We hypothesized that nirmatrelvir treatment during acute SARS-CoV-2 infection reduces risk of developing Long COVID and rebound after treatment is associated with Long COVID.

Methods: Observational cohort study within the Covid Citizen Science (CCS) study, an online cohort study with over 100,000 participants. We included vaccinated, non-hospitalized, non-pregnant individuals who reported their first SARS-CoV-2 positive test March-August 2022. Oral nirmatrelvir/ritonavir treatment was ascertained during acute SARS-CoV-2 infection. Patient-reported Long COVID symptoms, symptom rebound and test-positivity rebound were asked on subsequent surveys at least 3 months after SARS-CoV-2 infection.

Results: 4684 individuals met the eligibility criteria, of whom 988 (21.1%) were treated and 3696 (78.9%) were untreated; 353/988 (35.7%) treated and 1258/3696 (34.0%) untreated responded to the Long COVID survey (n=1611). Among 1,611 participants, median age was 55 years and 66% were female. At 5.4±1.3 months after infection, nirmatrelvir treatment was not associated with subsequent Long COVID symptoms (OR 1.15; 95%CI 0.80–1.64; p=.45). Among 666 treated who answered rebound questions, rebound symptoms or test positivity were not associated with Long COVID symptoms (OR 1.34; 95%CI 0.74–2.41; p=.33).

Conclusions: Within this cohort of vaccinated, non-hospitalized individuals, oral nirmatrelvir treatment during acute SARS-CoV-2 infection and rebound after nirmatrelvir treatment were not associated with Long COVID symptoms more than 90 days after infection.

Keywords

nirmatrelvir; post-acute sequelae of COVID-19; Long COVID; rebound; Paxlovid

Introduction

Symptoms after SARS-CoV-2 may persist as Long COVID, a type of post-acute sequalae of SARS-CoV-2 infection (PASC) defined as unexplained symptoms attributed to COVID-19 [1]. Vaccination reduces but does not eliminate risk of Long COVID [2]. Higher acute viral load or prolonged shedding may be associated with increased risk [3,4]. Recent studies suggest viral persistence in a subset of individuals with PASC, including prolonged gastrointestinal shedding, ongoing Spike and Nucleocapsid antigen in neuronal and astrocytic exosomes, and evidence of persistent viral RNA or proteins in deep tissues and plasma [5–10].

Among high-risk, unvaccinated, non-hospitalized individuals with symptomatic COVID-19, nirmatrelvir, a novel orally-administered SARS-CoV-2 main protease (M_{pro}) inhibitor in combination with ritonavir reduces viral load and progression to severe disease [11]. Anecdotal reports suggest that nirmatrelvir may improve Long COVID symptoms [12–14]. However, whether treatment with nirmatrelvir during acute infection reduces post-COVID conditions is uncertain, with two studies finding conflicting results in the same population[15,16]. Use of EHR-based diagnosis of post-COVID conditions, as in those studies, relies on patient reporting and clinician documentation of medical diagnoses so may not capture the possible treatment effect on Long COVID symptoms. A third study, which surveyed individuals 4 months after SARS-CoV-2 infection, found no association between nirmatrelvir use and prevalent Long COVID symptoms, but reported a prevalence of symptoms of nearly 50% in both groups [17].

Therefore, the objectives were to test the hypothesis that nirmatrelvir treatment during acute SARS-CoV-2 infection is associated with a lower prevalence of patient-reported Long COVID symptoms >90 days after infection, and that rebound of acute symptoms or rebound test-positivity after treatment is associated with higher prevalence of Long COVID symptoms.

Methods

Design, Setting, and Participants

The COVID-19 Citizen Science (CCS) Study is an online cohort study hosted on the Eureka Research Platform [18]. Recruitment occurred through email invitations to existing Eureka participants, referrals from partner organizations, and word of mouth. To participate, individuals must register for an account, agree to participate in English and provide electronic consent. After consenting, participants complete baseline and follow-up surveys. We used data collected from March 26, 2020, to December 22, 2022. We included individuals who enrolled prior to first known SARS-CoV-2 infection first infected when nirmatrelvir was available in March 2022 through August 2022. Outcomes were ascertained only for those who responded to surveys about Long COVID symptoms in November and December 2022. The primary outcome was defined as at least one patient-reported Long COVID symptom >90 days after acute SARS-CoV-2 infection [1].

Inclusion and Exclusion Criteria

We included CCS participants enrolled March 2020-August 2022 (median March 2021, IQR August 2020-September 2021) with first-reported positive SARS-CoV-2 antigen or PCR test starting in March 2022. We excluded those treated with molnupiravir, remdesivir, and monoclonal antibodies. Following the Emergency Use Authorization, we excluded hospitalized and pregnant individuals. Because >98% were vaccinated prior to infection we limited analysis to vaccinated individuals. We chose not to limit inclusion to “eligible” patients as in our clinical experience the “high risk” criteria are loosely interpreted but conducted sensitivity analyses limiting inclusion criteria to those defined as at high-risk by the Centers for Disease Control (CDC).

Exposures

The primary exposure was self-reported nirmatrelvir treatment within 30 days of first reported positive SARS-CoV-2 antigen or PCR test on a weekly survey from March 2022-August 2022. Participants who reported taking nirmatrelvir were subsequently invited to respond to a survey in December 2022 to assess for rebound symptoms or test positivity. Rebound symptoms were defined as symptom worsening after initial improvement. Rebound test positivity was defined as testing negative and then positive on antigen test after completing treatment.

Outcomes

The primary outcome was ≥1 self-reported prevalent Long COVID symptom >90 days after first SARS-CoV-2 positive test on a cross-sectional survey distributed in November and December 2022 that asked about presence, duration, and severity of Long COVID symptoms using a published non-validated instrument.[19] We decided a priori to use the 90-day World Health Organization definition as a significant proportion experience symptom resolution in the 4 week to 90 day period [19]. Symptoms queried included fatigue, shortness of breath, confusion, headache, altered taste and smell, joint pain, muscle aches, cough, chest pain, scratchy throat, nausea, vomiting, diarrhea, fever, chills, red or painful eyes, sore throat, and other. Because the survey was developed initially based on symptoms during acute COVID-19 prior to thorough understanding of common Long COVID symptoms, the queried symptoms do not include every symptom reported in Long COVID (brain fog and post-exertional malaise are excluded, for example), but the inclusion of an “other” symptom question helps overcome this limitation. Severity was assessed using a Likert-scale asked for each symptom (1–5, very mild to very severe).

Covariates

Other variables were self-reported including demographics, medical history, vaccine history, and lifestyle factors [19]. Only body mass index (BMI) had >1% of data missing (650 missing, 40%). For the propensity adjusted model, we imputed missing BMI from age, sex, race/ethnicity, and past medical history.

Statistical Analysis

The analysis plan was developed prior to outcome data collection and was designed to emulate a randomized clinical trial using a “target trial” approach [20]. First, we compared treated and untreated individuals using Chi-squared tests for categorical variables and T-tests for continuous variables. We modeled nirmatrelvir use propensity with logistic regression models including all individuals who met the inclusion/exclusion criteria including age, sex, race, ethnicity, socioeconomic status, education, employment, past medical history, substance use, number of vaccines. After checking the Hosmer-Lemshow goodness of fit and balance of key covariates by propensity score quintile, we used logistic regression models to model the association between nirmatrelvir and Long COVID among survey respondents adjusted for age, sex, time since SARS-CoV-2 test positivity, and the cubic spline of the propensity score. As a sensitivity analysis, we repeated the analysis using inverse probability of treatment weighting, truncating extreme weights >95th percentile. As

a post-hoc sensitivity analysis we restricted the inclusion criteria to United States residents at risk for severe COVID-19 defined according to the CDC using two definitions (age ≥50, one or more comorbid condition, or BMI≥25 kg/m^2; age ≥65, one or more comorbid condition, or BMI≥30 kg/m^2). The next post-hoc sensitivity analyses used propensity matching to estimate the average treatment effect using 1:1 nearest neighbor matching by propensity score or by Mahalanobis distance (inverse sample covariate covariance). For analyses of rebound, we used Fisher's exact test and logistic regression for unadjusted analyses given the lack of evident confounders. Analyses were conducted in SAS version 9.4 and STATA 17.0.

Results Reporting and Informed Consent

Results are reported in accordance with STROBE guidelines [21]. All participants provided digitally-signed informed consent. The study was reviewed and approved by the UCSF Institutional Review Board (#17–21879).

Results

Within the CCS, 4684 eligible vaccinated individuals reported their first positive SARS-CoV-2 test during the study period (Omicron era), of whom 988 (21.1%) were treated with nirmatrelvir and 3696 (78.9%) were untreated (Figure 1). Among those eligible, 353/988 (35.7%) treated and 1258/3696 (34.0%) untreated individuals responded to the Long COVID survey at 5.4±1.3 months after acute infection. Baseline characteristics and time since SARS-CoV-2 infection were similar among respondents and nonrespondents (Supplemental Table 1). As expected based on prescribing guidelines [22], individuals treated with nirmatrelvir were older, more likely to be male, and had more comorbidities (Table 1).

Association of nirmatrelvir/ritonavir treatment with Long COVID symptoms

Among those treated with nirmatrelvir, 57/353 (16.1%) reported Long COVID symptoms compared to 176/1258 (14.0%) untreated (OR 1.18; 95%CI 0.84–1.65; p=.31; Table 2). Commonly reported symptoms included fatigue, shortness of breath, confusion, headache, and altered taste and smell. The propensity score successfully modeled probability of treatment, and overall characteristics were similar by propensity score quintile (Supplemental Tables 2 & 3, Supplemental Figure). In the propensity-adjusted model, nirmatrelvir was not associated with self-reported Long COVID symptoms (OR 1.15; 95%CI 0.80–1.64; p=.45; Figure 2). Results were similar when incorporating demographics, past medical history, and substance use (OR 1.17; 95%CI 0.81–1.69). Similarly, using inverse probability of treatment weighting as an alternative analytic strategy yielded the same estimate (OR 1.17; 95%CI 0.80–1.71). Restricting to those at high risk yielded similar results for sensitive (n=968 treated & n=3,326; OR 1.11; 95%CI 0.77–1.59) and specific definitions (n=890 treated & n=2,840 untreated); OR 1.12, 95%CI 0.78–1.60). Finally, among those at high risk for severe COVID-19 we estimated average treatments effects of 0.032 (95%CI −0.017–0.081; p=.20) using propensity matching and 0.012 (95%CI −0.04–0.07; p=.67) using nearest neighbor matching, both consistent with no benefit of treatment.

Among those treated with nirmatrelvir reporting at least one Long COVID symptom, the median number of Long COVID symptoms was 1 (IQR 1–4) compared to 2 (IQR 1–4) among those untreated (p=.35); the mean number of symptoms was 2.86±2.42 and 3.06±2.54, respectively (p=.70). Few reported at least one severe or very severe Long COVID symptom in either group: 6 (1.7% overall, 10.5% with Long COVID) among the treated and 18 (1.4% overall, 10.2% with Long COVID) among the untreated (p=.18); therefore, we could not exclude an effect on symptom severity.

Rebound

Among 666 individuals treated with nirmatrelvir who responded to the rebound survey, 139 of the 650 who experienced symptomatic improvement during nirmatrelvir treatment (21%) reported rebound symptoms. Among those who repeated antigen testing after testing negative and completing treatment, 97/377 (25.7%) reported rebound test positivity. In total, 174/666 (26.1%) reported rebound symptoms or test positivity. In total 634 of the respondents to the rebound survey also responded to the Long COVID questions: 166 with rebound and 468 without rebound. Among those with rebound, 18/166 (10.8%) reported 1 or more Long COVID symptom compared to 39/468 (8.3%) without rebound (OR 1.34; 95%CI 0.74–2.41; p=.33; Table 3). Results were similar for symptoms (9.9% vs 8.4%; OR 1.20; 95%CI 0.62–2.31) and test positivity (10.8% vs 7.7%; OR 1.45; 95%CI 0.66–3.21). Results were similar using a more sensitive outcome of those who had not experienced full recovery (14.9% with rebound vs 12.8% without; OR 1.20; 95%CI 0.73–1.96). Results were similar restricting analyses only to those who reported completing the full ten-dose course of nirmatrelvir (n=621): OR 1.20 (95% CI 0.62–2.30; p=.59).

Results were similar limiting analysis to respondents who completed treatment more than 90 days prior (n=157). Of those, 31/157 (20.2%) experienced rebound symptoms and 17/84 (19.7%) had a rebound positivity with 38/157 (24.2%) classified as having any rebound. Only 2/38 (5.2%) individuals who experienced rebound reported Long COVID symptoms compared to 19/119 (16.0%) who did not experience rebound (p=.11). Among those who experienced rebound test positivity, none reported Long COVID symptoms compared to 10/67 (14.9%) without rebound test positivity (p=.20).

Discussion

Within an online observational cohort, treatment with nirmatrelvir among vaccinated, non-hospitalized individuals during first known SARS-CoV-2 infection was not associated with a lower prevalence of patient-reported Long COVID symptoms >90 days after infection. Treatment was not associated with fewer Long COVID symptoms or severe symptoms, although these endpoints were limited by rarity of these outcomes. Rebound symptoms or test positivity after nirmatrelvir treatment were not associated with Long COVID symptoms.

Prior studies of nirmatrelvir, including two randomized clinical trials, EPIC-HR and EPIC-SR, focused on acute outcomes of SARS-CoV-2 infection among unvaccinated individuals. EPIC-HR demonstrated a reduction in hospitalization and mortality by day 28 among those at high risk of disease progression treated with nirmatrelvir compared to placebo [11], but the EPIC-SR study of standard risk individuals was stopped early for lack of

benefit with negative results now posted on clinicaltrials.gov but not published [23]. "Real-world" observational studies have found similar results, with reductions in hospitalization and mortality among higher risk and vaccinated individuals.[24–29] Higher viral loads and prolonged viral shedding have been associated with risk of Long COVID [3,4], and nirmatrelvir results in faster viral clearance [30,31], supporting the hypothesis that nirmatrelvir may prevent Long COVID. Secondly, in this cohort, the number of symptoms during acute infection is associated with Long COVID symptoms independent of vaccination and variant wave [19], but whether reducing acute symptoms with antiviral therapy prevents Long COVID has not been demonstrated.

Three prior studies have considered the effect of nirmatrelvir during acute infection on EHR-ascertained post-COVID outcomes. Two found contradictory results despite both including Veterans and examining EHR-diagnosed post-COVID conditions by ICD-10 diagnostic codes as the outcome of interest [15,16]. Bajema et al found that nirmatrelvir improved 30-day outcomes but not EHR-diagnosed post-COVID conditions at 6 months, whereas Xie et al found decreased post-COVID conditions, hospitalizations, and mortality among treated individuals from 30–90 days. Similar to our design, Bajema et al used a target-trial emulation study design, which is more robust to common pitfalls of observational studies of treatment effects. Both included an older, mostly male patient population with significant comorbidities and are limited by differential outcome ascertainment, differential misclassification, and lack of ascertainment that ICD-codes correspond to symptoms. A third study, by Patel et al, used EHR records from the TriNetX research network, but included individuals with pre-existing Long COVID in the control group which may explain their finding of a benefit of nirmatrelvir [32].

In contrast to EHR-based studies focused on ascertainment of post-COVID-conditions using ICD-10 codes, our study evaluated whether nirmatrelvir is associated with patient-reported symptoms. Patient-reported symptoms is a closer approximation of the condition of interest (Long COVID, defined as unexplained symptoms persisting for >90 days following initial infection) [1]. One other published study surveyed participants from a single medical center four months after SARS-CoV-2 infection and compared the prevalence of self-reported prevalent Long COVID symptoms among people who reported nirmatrelvir use to those who were not treated with nirmatrelvir [17]. Our findings are consistent with their finding of no association between nirmatrelvir use and subsequent Long COVID symptoms. Our inclusion of participants already enrolled in the COVID Citizen Science study without prior infection, use of a target-trial framework, and propensity-adjustment further strengthens the validity of our findings. In sum, our finding that nirmatrelvir treatment during acute infection is not associated with lower odds of Long COVID is consistent with the Bajema report of no difference in post-COVID conditions at 6 months [16] and with the Congdon survey study at 4 months after infection [17].

We found a higher proportion with clinical rebound than previously reported [33,34,35], but did not identify an effect of post-treatment rebound on Long COVID symptoms. Since antivirals entered widespread use, there has been intense interest in this phenomenon, and a case report suggested the development of Long COVID among those with post-treatment rebound [12]. The observation that antiviral-associated rebound is not associated with Long COVID

suggests that the potential for treatment-related rebound should not discourage antiviral use, and that individuals experiencing this phenomenon are not at elevated risk for Long COVID. Rebound test positivity was common in the early days of the pandemic [36]; we were not able to determine whether rebound unrelated to treatment increases risk of Long COVID.

Our study does not consider whether nirmatrelvir may be effective at treating (rather than preventing) Long COVID, which is currently under investigation in one ongoing and two planned clinical trials (NCT05576662, NCT05595369, NCT05668091).

Limitations

The primary limitations arise from its observational nature which is at risk for selection bias and confounding. The cohort was relatively homogeneous; most individuals identified as White with advanced education, in large part because we limited this study to those privileged enough to avoid infection until March 2022. We relied on self-report of treatment and Long COVID symptoms. Baseline data was collected prior to infection, and SARS-CoV-2 testing and nirmatrelvir use were collected at the time of testing and treatment, respectively, limiting the impact of recall bias. Nonetheless differential reporting of test positivity or survey response (which was non-differential by treatment) may induce selection bias. The survey did not include all Long COVID symptoms, such as post-exertional malaise, insomnia, decreased exercise tolerance, and menstrual cycle changes, for example. Our study differs from EHR-based reports in that we assessed Long COVID symptoms rather than ICD-10 codes. We therefore could not determine whether treatment had an impact on post-acute diagnoses. We also did not include objectively measured post-COVID outcomes (e.g., exercise capacity [37], neurocognitive performance [38], or other measurable physiologic perturbations). We used propensity scores and inverse probability of treatment weighting to adjust for baseline differences between propensity of treatment between the treated and untreated, but residual confounding may still bias the results. Rebound testing was not performed systematically, and results were based on participant test self-report.

Conclusions

Among vaccinated, non-hospitalized adults in the COVID Citizen Science online cohort, nirmatrelvir treatment during acute SARS-CoV-2 infection was not associated with Long COVID symptoms >90 days after infection. Among those treated, rebound was not associated with Long COVID symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

Data are available by application to the COVID Citizen Science leadership committee. Data may be requested by emailing covid19@eurekaplatform.org.

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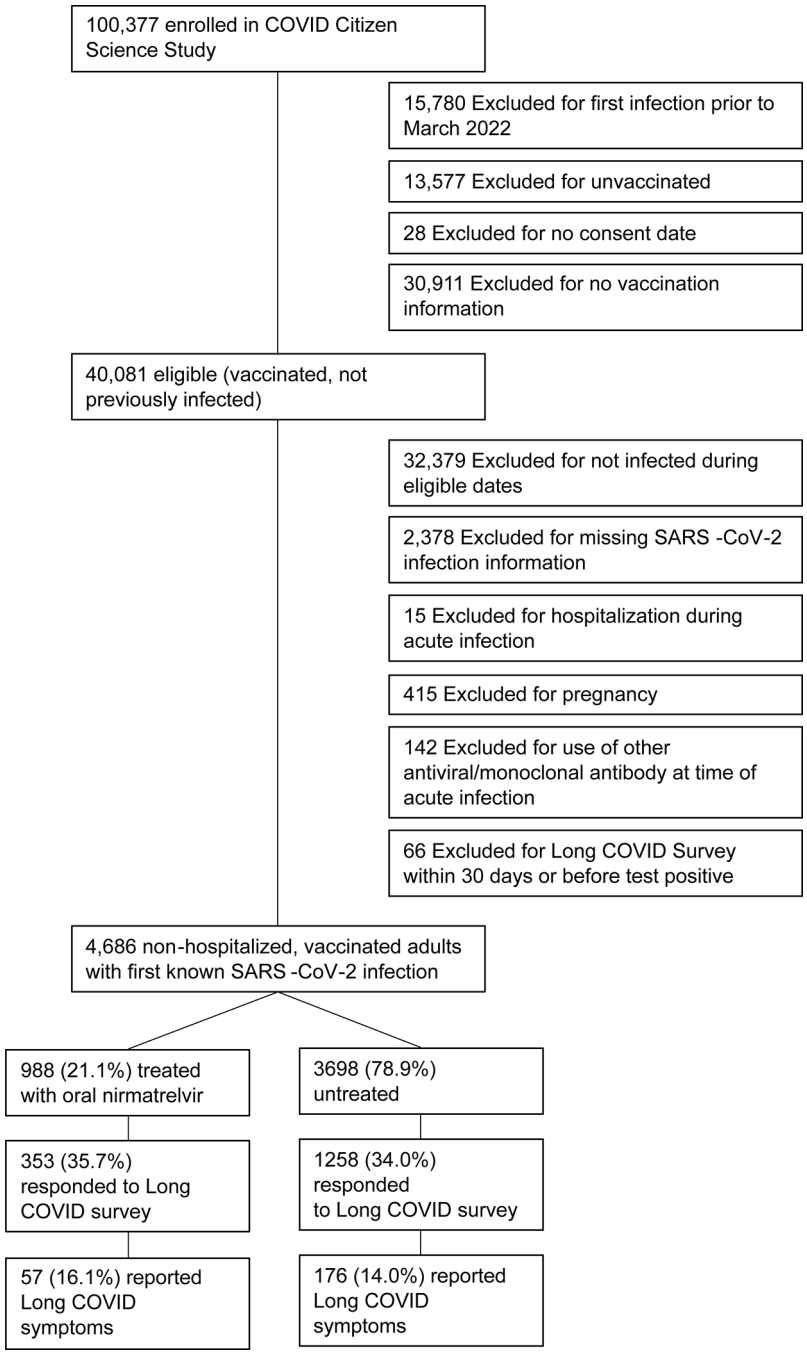

Figure 1.
Flow diagram for participants included in the primary analysis.

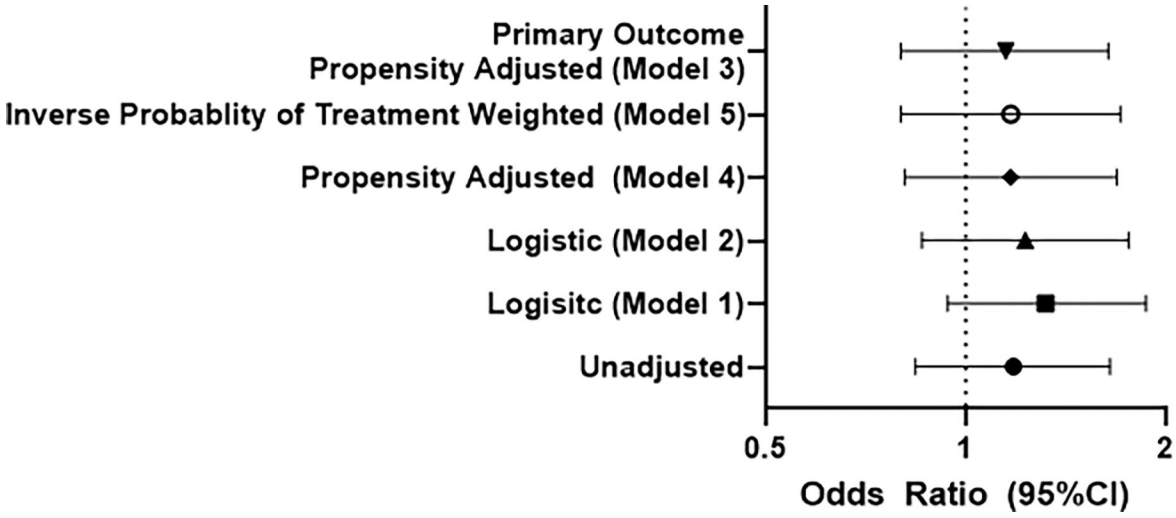

Figure 2.

In all models, treatment with oral nirmatrelvir was not associated with lower odds of patient reported Long COVID symptoms with confidence intervals that cross 1, which suggests that treatment is not beneficial in reducing the risk of Long COVID. Model 3, the pre-specified primary result, includes age, sex, and time since SARS-CoV-2 infection, and the restricted cubic spline of the propensity score. Model 1 includes age, sex, and time since SARS-CoV-2 infection. Model 2 includes age, sex, time since SARS-CoV-2 infection, race/ethnicity, past medical history and substance use. Model 4 is the propensity-adjusted version of Model 2. Finally, Model 5 incorporates inverse probability of treatment weighting and age, sex, and time since SARS-CoV-2 infection. Results were similar in additional sensitivity analyses.

Table 1

Baseline characteristics among Long COVID survey respondents. For race and ethnicity, participants could select all that apply so these are not mutually exclusive categories.

	Treated with nirmatrelvir/ritonavir, N = 353		SARS-CoV-2 infected, untreated, N = 1258		
Characteristic	**N**	**Mean ± std or n (%)**	**N**	**Mean ± std or n (%)**	**P value treated vs not**
Age	352	62.1 ± 12.7	1258	55.1 ± 13.6	0.0000
Female sex assigned at birth	349	186 (53.3%)	1250	811 (64.9%)	0.0001
Race/Ethnicity*					
White	347	327 (94.2%)	1245	1156 (92.9%)	0.37
Black or African American	347	4 (1.2%)	1245	28 (2.2%)	0.20
Asian	347	14 (4.0%)	1245	61 (4.9%)	0.50
Native Hawaiian or Pacific Islander			1245	1 (0.1%)	0.60
American Indian or Alaska Native	347	5 (1.4%)	1245	17 (1.4%)	0.92
Other/Dont' know	347	7 (2.0%)	1245	29 (2.3%)	0.73
Hispanic Ethnicity	349	11 (3.2%)	1250	73 (5.8%)	0.05
Highest Educational Level					0.28
No high school degree	349	2 (0.6%)	1250	1 (0.1%)	
High school graduate	349	7 (2.0%)	1250	25 (2.0%)	
College degree	349	151 (43.3%)	1250	587 (47.0%)	
Graduate degree	349	187 (53.6%)	1250	628 (50.2%)	
Other	349	2 (0.6%)	1250	9 (0.7%)	
MacArthur Socioeconomic Status	349	7.23 ± 1.55	1249	7.17 ± 1.47	0.46
US resident	353	353 (100.0%)	1258	1220 (97.0%)	0.001
Body Mass Index	216	27.9 ± 6.5	745	27.6 ± 6.0	0.50
Tobacco use	353	10 (2.8%)	1258	55 (4.4%)	0.19
Marijuana use	353	23 (6.5%)	1258	87 (6.9%)	0.79
Alcoholic drinks/week pre-COVID	353	4.52 ± 5.48	1254	4.59 ± 5.77	0.85
Financial insecurity pre-COVID	352	61 (17.3%)	1250	200 (16.0%)	0.55
Average Anxiety (GAD-7) pre-COVID	352	3.27 ± 3.70	1250	3.55 ± 3.55	0.20
Average Depression (PHQ-8) pre-COVID	352	3.32 ± 3.71	1250	3.58 ± 3.59	0.24
Hypertension	353	128 (36.3%)	1257	364 (29.0%)	0.01
Diabetes	353	30 (8.5%)	1257	69 (5.5%)	0.10
Coronary Artery Disease	353	23 (6.5%)	1257	62 (4.9%)	0.24
Heart Failure	353	3 (0.8%)	1257	15 (1.2%)	0.10
Stroke or Transient Ischemic Attack	353	12 (3.4%)	1257	23 (1.8%)	0.12
Atrial Fibrillation	353	27 (7.6%)	1257	54 (4.3%)	0.04
Sleep Apnea	352	69 (19.6%)	1257	154 (12.3%)	0.001
Chronic Obstructive Pulmonary Disease	353	7 (2.0%)	1257	18 (1.4%)	0.76

	Treated with nirmatrelvir/ritonavir, N = 353		SARS-CoV-2 infected, untreated, N = 1258		
Characteristic	**N**	**Mean ± std or n (%)**	**N**	**Mean ± std or n (%)**	**P value treated vs not**
Asthma	353	37 (10.5%)	1257	79 (6.3%)	0.02
Cancer	353	41 (11.6%)	1257	78 (6.2%)	0.0006
Immunodeficiency	353	17 (4.8%)	1257	12 (1.0%)	0.0000
HIV	353	3 (0.8%)	1257	8 (0.6%)	0.79
Anemia	353	26 (7.4%)	1257	121 (9.6%)	0.33
Days since COVID-19	353	162 ± 40	1258	165 ± 45	0.16
Number of acute symptoms	353	5.05 ± 2.20	1250	4.91 ± 2.27	0.31
Number of Long COVID Symptoms among those with any, median (IQR)	57	1 (IQR 1–4)	176	2 (IQR 1–4)	0.35
Number of SARS-CoV-2 vaccines received prior to COVID-19	353	2.41 ± 0.62	1258	2.46 ± 0.61	0.25
Number of Vaccines received after COVID-19	353	0.01 ± 0.09	1258	0.00 ± 0.07	0.41

Table 2

This table reports the number and percentage among the treated and untreated who did and did not report Long COVID symptoms.

	Not treated	Nirmatrelvir treated	Total
No Long COVID symptoms	1082 (86.0%)	176 (83.9%)	1258 (85.5%)
≥1 Long COVID symptom	296 (14.0%)	57 (16.1%)	353 (14.5%)
Total	1378 (100%)	233 (100%)	1611 (100%)

Table 3

Among 634 who responded to questions about rebound and Long COVID, although 26% experienced rebound symptoms, rebound test positivity, or both, there was not a statistically significant difference in the presence of Long COVID among those who experienced rebound compared to those who did not (OR 1.34; 95%CI 0.74–2.41; p=.33).

	No Rebound	Rebound Symptoms or Test Positivity	Total
No Long COVID symptoms	429 (91.7%)	148 (90.2%)	577 (91.0%)
≥1 Long COVID symptom	39 (8.3%)	18 (10.8%)	57 (9.0%)
Total	468 (73.8%)	166 (26.2%)	634 (100%)