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The Impact of Nirmatrelvir-Ritonavir in Reducing Hospitalizations Among High-Risk Patients with SARS-Cov-2 During the Omicron Predominant Era

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ABSTRACT

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has caused significant morbidity and mortality in high-risk populations. Several therapeutics have been developed to reduce the risk of COVID-19 related complications, hospitalizations, and death. In several studies, nirmatrelvir-ritonavir (NR) was reported to reduce the risk of hospitalizations and death. We aimed to evaluate the efficacy of NR in preventing hospitalizations and death during the Omicron predominant period.

METHODS: We retrospectively evaluated patients from June 1, 2022, through September 26, 2022. There was a total of 25,939 documented COVID-19 cases. Using propensity matching, we matched 5,754 NR treated patients with untreated patients.

RESULTS: Post-matching, the median age of the nirmatrelvir-ritonavir (NR) treated group was 58 years (interquartile range [IQR], 43–70 years) and 42% were vaccinated. Post-matching composite outcome of the 30-day hospitalization and mortality in the NR treated group were 0.9% (95%: CI 0.7% to 1.2%) vs. 2.1% (95% CI: 1.8% to 2.5%) in the matched control group, with a difference of -1.2 (-1.7, -0.8), P-value <0.01. The difference rates (NR vs. control) in 30-day all-cause hospitalizations and mortality were -1.2% (95% CI: -1.6% to -0.7%, p-value <0.01) and-0.1% (95% CI, -0.2% to 0.0%, P value= 0.29), respectively. We found similar finding across different age groups (≥65 vs. <65) and the vaccinated group.

CONCLUSION: We report a significant benefit with the use of NR in reducing hospitalizations among various high-risk COVID-19 groups during the Omicron BA.5 predominant period.

KEYWORDS: COVID-19; Omicron variant; nirmatrelvir-ritonavir

INTRODUCTION:

The coronavirus disease 2019 (COVID-19) pandemic has caused a significant number of deaths in the United States (US) and globally. With ongoing worldwide infections, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to inflict high-risk populations with significant mortality and morbidity through the emergence of new variants from resulting random mutations that evade immunity (1). In November 2021, the Omicron variant became the dominant SARS-CoV-2 globally and was identified as a variant of concern (VOC). Subsequently, the subvariants BA.1, BA.1.1, and BA.2 were reported in 2022. Most recently, the subvariants BA.4, BA.5, and later subvariants BA.2.75, BA.4.6, BF.7, BQ.1, and BQ.1.1 were reported in the US and deemed non-susceptible to anti-SARS-CoV-2 neutralizing anti-spike monoclonal antibodies (mAbs) (2, 3, 4, 5). As a result, the Food and Drug Administration (FDA) revoked the bebtelovimab Emergency Use Authorization (EUA) on November 30, 2022 (6). Nirmatrelvir, an oral protease inhibitor active against the viral protease M^{PRO}, which is important in viral replication through the cleavage of the two viral polyproteins, has potent antiviral activity against all human coronaviruses. When administered with ritonavir, nirmatrelvir therapeutic concentrations are increased (7, 8, 9). A randomized controlled trial of nirmatrelvir-ritonavir (NR), brand name Paxlovid in non-hospitalized, high-risk, SARS-CoV-2 non-immune adults provided the data for the FDA EUA approval of NR during the B.1.617.2 (delta) variant predominant period (10, 11). In December 2021, the FDA issued an EUA for the use of NR in the treatment of mild-to-moderate COVID-19 in high-risk patients (7, 8, 9). In a recent study during the Omicron variant surge, rates of COVID-19 related hospitalizations and deaths were significantly lower in adults 65 years of age or older treated with NR than among younger patients who had received such treatment, regardless of previous SARS-CoV-2 immunity (12). Moreover, several studies had reported on the effective prevention of hospitalizations and deaths using MAbs in high-risk patients (13, 14, 15). Meanwhile, spike protein mutations in SARS-CoV-2 Omicron subvariants resulted in the reduced susceptibility of previously authorized MAbs such as bamlanivimab-etesevimab,

casirivimab-imdevimab, and sotrovimab. Therefore, on February 11, 2022, the FDA granted EUA for bebtelovimab (BEB) as an alternative therapy for high-risk patients with mild to moderate COVID-19 (16, 17, 18, 19, 20).

In a recent real-world study of BEB, researchers evaluated high-risk outpatients during the predominantly SARS-CoV-2 Omicron BA.2 subvariants period and compared outcomes to those treated with NR. According to the authors, the rate of progression to severe disease after treatment with BEB did not result in a significant difference when compared to the NR-treated group. This led to the use of BEB as a valuable option for high-risk patients for whom NR use may have been challenging at the time (21). Based on the results of this study and the National Institutes of Health (NIH) recommendations at the time, many centers including ours used BEB in patients at risk for NR-associated drug interactions and adverse reactions such as in solid organ transplant recipients (22). However, after the FDA revoked the BEB EUA on November 20, 2022, oral antivirals and remdesivir became the only viable treatment options for patients at-risk for severe COVID-19 infections (5, 6). Therefore, we aimed to evaluate the 30-day all-cause hospitalization and/or mortality in patients with mild to moderate COVID-19 treated with NR in our hospitals and clinics. Furthermore, we evaluated these outcomes among vaccinated, immunocompromised, and elderly (≥65 years of age) patients.

METHODS:

This study was approved by the Institutional Review Board of the University of Arizona with a waiver of patient consent, given the retrospective nature of the study. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Overview

This study is an observational retrospective cohort analysis of patients with COVID-19 from June 1, 2022, through September 24, 2022. The patient follow-up date was censored on October 24, 2022. NR-prescribed patients and untreated patients were captured from electronic health records (EHR) in the Banner Health Care System (a non-profit, large health care organization), which houses thirty hospitals and several clinics across the western US. High-risk patients with mild to moderate COVID-19 infection within five days of symptoms onset may be prescribed NR under the FDA EUA (https://www.bannerhealth.com/staying-well/health-and-wellness/wellness/covid/treatment). Oral antivirals and remdesivir are currently available treatment options since the FDA revoked bebtelovimab EUA on November 30, 2022 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region).

A total of 42,895 outpatient COVID-19 positive (positive PCR or direct antigen tests) patients were selected from the Banner Cerner-EHR. Exclusion criteria included age less than 18 years, those in hospice, emergency room, or inpatient settings, receipt of tixagevimab-cilgavimab injection or bebtelovimab infusion, molnupiravir use prior to the index date, and/or weight less than 40 kilograms (Figure 1). The resulting study cohort included 5,772 NR-prescribed patients and 20,167 untreated patients in the Banner system. The study index date for cohorts was determined as the date of the completed NR prescription date or the date of the first positive COVID-19 test. The index dates were used as enrollment dates for the study. Demographic and clinical covariates of both cohorts were extracted from the EHR for propensity matching and analysis (Table 1). The clinical covariates were derived from the Charlson Comorbidity Index. The post-match cohort consisted of 5,754 pairs (N= 11,508). Primary outcomes included the occurrence of 30-day all-cause hospitalization and/or mortality after the index date. For subgroup analysis, patients were grouped and rematched under vaccination status, immunocompromised status, and age (<65 or ≥65) categories. The rate of emergency room visits within 30 days of enrollment was considered a secondary outcome of the study.

Multivariable Propensity Matching

The cohorts were 1:1 propensity matched without replacement across 26 covariates. Since a randomization was not an option for this retrospective observational study, a propensity matching was performed to adjust for the difference between the treated and untreated cohorts to reduce covariate imbalances and to minimize selection bias. An optimal matching algorithm that minimizes the sum of the absolute pairwise distance across the matched sample was used for matching. This algorithm was determined best over the nearest neighbors and complete matching algorithms per the covariate balance and the count of unmatched individuals. A generalized linear model with a logistic regression link was used to calculate pairwise distances. Pairs were matched exactly based on vaccination status, BMI, age, and diabetes. (i.e., a fully vaccinated patient from the NR-prescribed cohort could only be matched to a fully vaccinated patient from the untreated cohort). The clinical (Charlson Comorbidity Index-based) variables, demographic covariates, and monthly time variable were included in the model to calculate the propensity score (PS). Post-match time variable balance showed that the index dates of treated and untreated cohorts were within a month of each other to account for monthly COVID-19 variant changes. Covariate balance was assessed by comparing pre- and post-match standardized mean differences (SMDs), reported in Table 1. MatchIt package from the statistical computing software R was used to build the propensity models.

Statistical Analysis

For each outcome, event count, percentage of the event and ninety-five percent confidence intervals were reported. Exact McNemar's test was used to compute the percent difference between the prescribed and untreated groups. P-values of the test were reported. P values less than 0.05 were considered statistically significant. For subgroup analysis, vaccination status (fully vaccinated: yes or no), immunocompromised status (malignancy, lymphoproliferative disorders, hematopoietic stem cell

transplant, solid organ transplantation, HIV: yes or no) and age (<65 vs. ≥65 years old) were assessed to compare the differences in primary outcomes. A patient was considered fully vaccinated (greater than two doses of mRNA vaccines) if at least 14 days passed before they were enrolled in the study. Using only the observations that were matched originally, cohorts were rematched within subgroups using the same propensity model (23).

RESULTS:

Patient Characteristics:

From June 1, 2022, through September 26, 2022, a total of 25,939 patients were diagnosed with COVID-19; of these, 5772 patients were treated with NR. Table 1 shows the baseline characteristics of the NR treated and untreated control cohorts before and after PS matching. All post-PS-matching covariate SMDs were below a 0.05 threshold, indicating an optimal matching and statistically insignificant differences among the variables between the two groups at baseline. In the post-PS-matched cohort, the median age of patients in the NR treatment arm was 58 years (interquartile range [IQR], 43–70 years); 60.1% were female, 71.1% were of the white race, and 42% were fully vaccinated. Some of the high-risk characteristics included age ≥60 years (44.8%), BMI ≥35 kg/m2 (24.3%), diabetes mellitus (23.4%), chronic lung disease (27.2%), kidney disease–any stage (4.7%), solid organ transplantation (0.3%), cancer (6.8%), and human immunodeficiency virus (HIV) disease (0.3%).

Primary and Secondary Outcomes:

The incidence of the composite outcome in the pre-PS matched NR, and untreated control cohorts were 0.9% and 1.8%, respectively (data not shown). Table 2 shows the results of the composite outcome within 30 days in the post propensity matched cohorts. Compared to the untreated control group, the incidence of patients with the composite outcome in the NR-treated group within 30 days is 0.9% (95%: CI 0.7% to 1.2%) vs. 2.1% (95% CI: 1.8% to 2.5%) (difference -1.2 [-1.7, -0.8], p-value <0.01). The difference rate (NR minus untreated control) in all-cause hospitalizations and mortality within 30 days were -1.2% (95% CI: -

1.6% to -0.7%, -value <0.01) vs -0.1% (95% CI, -0.2% to 0.0%, p-value= 0.29). Emergency room visits after the index date was lower in NR cohort compared with the untreated control cohort (difference -1.0% (95% CI: -1.6% to -0.3%, p-value <0.01). The number needed to treat (1/0.021-0.009) with NR was 83 to avoid one hospitalization and/or death over 30 days.

Subgroup Analysis:

Table 3 shows the primary composite outcomes for the propensity-matched NR-treated and untreated cohorts, stratified by vaccination status, immunocompromised status, and age. A significantly lower rate of primary outcome events occurred in both the vaccinated (% difference -1.0, [95% CI -1.7, -0.4], p <0.01) and unvaccinated (% diff -1.2, [95% CI -3.1, -1.0], p< 0.01) groups treated with NR compared to their untreated counterparts. Patients 65 age and older (% diff -1.9, [95% CI -2.9, -0.9], p< 0.01) and patients younger than 65 (% diff -0.8, [95% CI -1.3, -0.3], p< 0.01) experienced a significantly lower rate of primary composite events with NR. Immunocompetent patients treated with NR experienced fewer primary composite outcome events (% diff -1.2, [95% CI -1.6, -0.7], p< 0.01). However, NR treatment did not reach statistical significance in the rate of primary composite outcomes among immunocompromised patients (% diff -2.1, [95% CI -6.0, 1.7], p= 0.33), but the relative risk reduction of 44% is clinically meaningful.

DISCUSSION:

In the current study, we report on the efficacy of NR in reducing the risk of hospitalization among a large cohort of diverse matched patients during the COVID-19 Omicron variant predominant period. In addition, we found that this benefit persisted among different age and vaccination groups. Our secondary outcomes revealed a reduction in emergency department visits but not a reduction in the mortality rate. NR has been reported to reduce the rates of 28-day hospitalizations or death in high-risk patients with COVID-19 and therefore received the FDA's EUA approval (9). Since its approval, multiple

studies have reported on the efficacy of NR in reducing hospitalizations among COVID-19 patients (12, 24). However, in contrast to prior studies, our cohort included a large and diverse group of patients that were matched based on underlying characteristics and comorbidities.

Our cohort included patients during the Omicron variant predominant period (BA.2, BA.2.12.1, and BA.5). This is important to consider as the FDA withdrew the last available mAb, BEB, due to its reduced efficacy against Omicron variants on November 30, 2022 (6). Therefore, NR provides a preferable antiviral treatment option in outpatient settings, especially with the presumed lower efficacy of molnupiravir and the logistic challenges accompanying the administration of intravenous remdesivir in the outpatient settings (25, 26). Despite the reported lower rates of hospitalizations and mortality during the Omicron period (27), we have shown that there was a significant (~50%) reduction in the rates of hospitalizations with the use of NR. Therefore, the benefit of NR persisted in preventing hospitalizations in high-risk patients during this epidemiological shift.

In our study period, the 30 days mortality was very low at 0.1% among untreated groups compared to previous reports in the literature (27). While previous studies reported that NR reduced mortality mainly among elderly patients, we found that the benefits persisted across all age groups, which could be related to low mortality rates in our cohort. Moreover, while Arbel et al. concluded that NR was beneficial only among patients 65 years or older, the efficacy of NR in reducing rates of hospitalizations was statistically significant across different age groups in our study (12).

Immunocompromised patients are at the highest risk for COVID-19 complications due to their compromised immune response to infection, reduced immunogenicity, and increased risk of post-COVID-19 superimposed bacterial and fungal infections. Therefore, providing COVID-19 therapies in a timely manner can help reduce such complications. Indeed, in our cohort, the untreated immunocompromised patients had worse outcomes and higher percentages of complications compared

to the immunocompetent group. This was corroborated by another study of solid organ transplant recipients during the Omicron variants period (28). However, while NR reduced such complications, these results were not statistically significant. This is likely due to our small sample size of matched immunocompromised patients and potentially to the lower rates of NR prescriptions in this population (29).

COVID-19 vaccines have emerged as an effective method in reducing COVID-19 complications; however, with the emergence of SARS-CoV-2 variants, their effectiveness was shown to be reduced (30). In our study, we showed that NR led to a reduction in hospitalizations regardless of vaccination status. Most recent NR-related studies also report on the reduction in mortality among hospitalized and non-hospitalized vaccinated patients (31, 32).

Propensity matching cannot replace gold standard randomization process in clinical trials or account for unmeasured confounders, but it can reduce bias in estimating treatment effects in non-randomized observational data, such as ours. The propensity score is the probability of receiving a treatment of interest based on patient characteristics and clinical setting and is used to adjust for differences between groups (pseudo-randomization). Our post-match SMDs were below 0.10 (mostly <0.05) indicating acceptable matching. We believe that our propensity matching is optimal and high quality because it utilized a large sample size, matching based 26 covariates (and 4 exact matching), and the post-match SMDs being mostly <0.05 indicating perfect matching and adjustment for covariate imbalances.

The strengths of our study include the real-world experience in a very large population, matched based on multiple risk factors, which reduced confounding. Moreover, our study included an analysis of the effects of NR among vaccinated individuals. We investigated the outcome of emergency department visits separately from hospitalizations and death, which can help provide insight into the intervention's

cost-benefits. However, our study has several limitations, including the retrospective design, which could have biased data collection. This may be seen in the number of deaths and hospitalizations being lower than what has been reported by Arizona Department of Health Services. While patients have been prescribed NR, it is unknown from our dataset if they received the medication or adhered to therapy. Also, while we included vaccination status among different groups, we did not account for acquired immunity from previous infections or reduced immune responses secondary to the patients' underlying comorbidities. Lastly, while our data is obtained from a large hospital system, data outcomes of patients that were possibly hospitalized outside the banner health system and the state of Arizona are lacking.

In conclusion, we found that NR helps prevent COVID-19 hospitalization and emergency department visits in different high-risk groups. Moreover, beyond the reduction of COVID-19 complications, NR can help prevent healthcare systems from becoming overwhelmed with COVID-19 related visits and therefore permit non-COVID-19 cases to be treated adequately.

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Conflict of Interest: The authors declared no conflict of interest related to this research. Dr. M Al-Obaidi reported that he received an honorarium from Shionogi Inc. and La Jolla pharmaceuticals for serving in their advisory board meetings. Dr. Zangeneh has a research grant with AiCuris.

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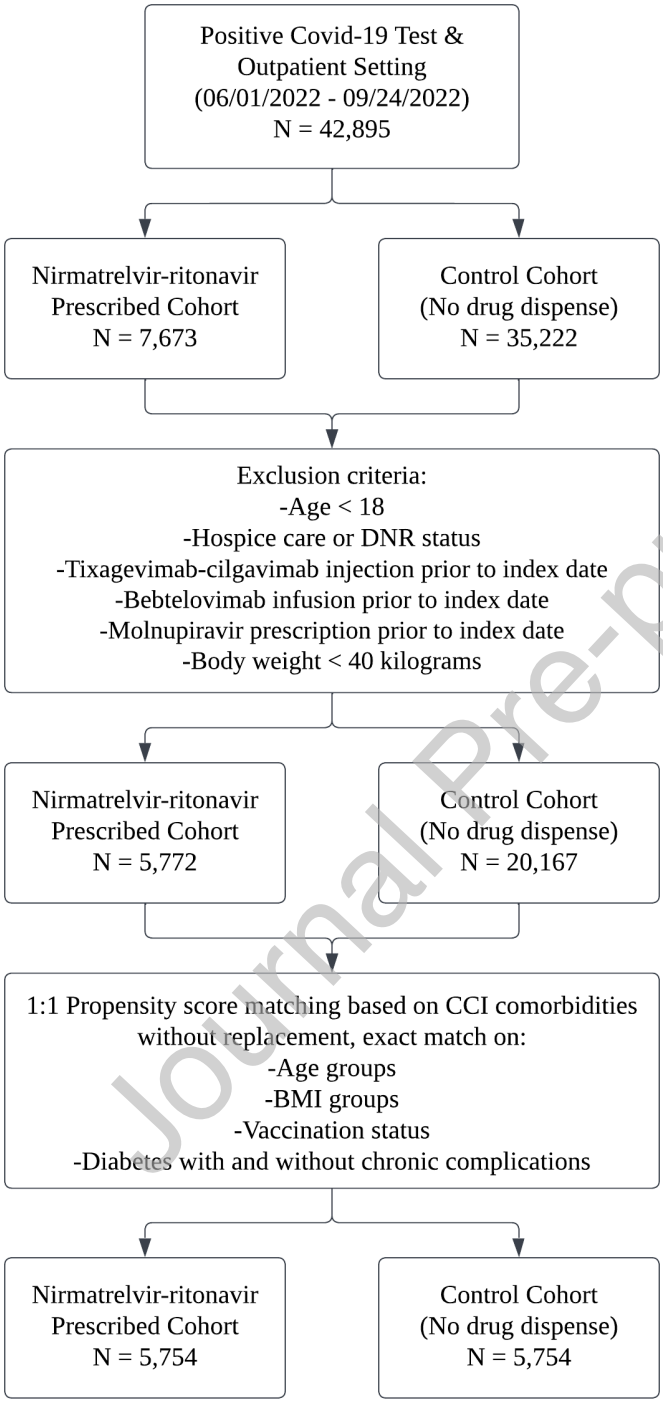
Clinical Significance:

- Coronavirus disease 2019 (COVID-19) infections continue to inflict high-risk populations with significant mortality and morbidity with the emergence of new variants resulting from random mutations that evade immunity.

- Several studies have reported a reduction in hospitalizations and death among patients treated with nirmatrelvir-ritonavir (Paxlovid).

- Despite the reported benefits of nirmatrelvir-ritonavir, greater healthcare provider awareness is required since many at-risk individuals are not being offered this important treatment option.

Figure 1. Flow chart



Tables:

Table 1: Patient characteristics and covariate balance before and after propensity matching.

	After Propensity Matching			Before Propensity Matching		
	Nirmatrelvir-Ritonavir Cohort	Untreated Control Cohort	SMD	Nirmatrelvir-Ritonavir Cohort	Untreated Control Cohort	SMD
	N=5,754	N=5,754		N=5,772	N=20,167	
Age	58.0 [43.0,70.0]	58.0 [42.0,70.0]		58.0 [43.0,70.0]	46.0 [31.0,63.0]	
Age Groups						
18-35	785 (13.6)	785 (13.6)	0.00	788 (13.7)	6572 (32.6)	-0.55
35-50	1348 (23.4)	1348 (23.4)	0.00	1355 (23.5)	4890 (24.2)	-0.02
50-60	1045 (18.2)	1045 (18.2)	0.00	1047 (18.1)	3013 (14.9)	0.08
60-70	1253 (21.8)	1253 (21.8)	0.00	1255 (21.7)	2662 (13.2)	0.21
>70	1323 (23.0)	1323 (23.0)	0.00	1327 (23.0)	3030 (15.0)	0.19
Sex						
Male	2295 (39.9)	2396 (41.6)	-0.04	2300 (39.8)	7844 (38.9)	0.02
Fully Vaccinated						
Yes	2418 (42.0)	2418 (42.0)	0.00	2422 (42.0)	7756 (38.5)	0.07
No	2080 (36.1)	2080 (36.1)	0.00	2088 (36.2)	6560 (32.5)	0.08
Unknown	1256 (21.8)	1256 (21.8)	0.00	1262 (21.9)	5851 (29.0)	-0.17
Race/Ethnicity						
White	4090 (71.1)	4007 (69.6)	0.03	4103 (71.1)	12652 (62.7)	0.18
Black	240 (4.2)	281 (4.9)	-0.04	242 (4.2)	1183 (5.9)	-0.08
Hispanic	827 (14.4)	758 (13.2)	0.03	829 (14.4)	4009 (19.9)	-0.16
Asian/Pacific Islander	101 (1.8)	108 (1.9)	-0.01	101 (1.7)	358 (1.8)	-0.00
Native American/Alaskan	66 (1.1)	54 (0.9)	0.02	67 (1.2)	250 (1.2)	-0.01
Unknown	430 (7.5)	546 (9.5)	-0.08	430 (7.4)	1715 (8.5)	-0.04
BMI Group						
≤20	143 (2.5)	143 (2.5)	0.00	146 (2.5)	897 (4.4)	-0.12
20-25	1000 (17.4)	1000 (17.4)	0.00	1001 (17.3)	4340 (21.5)	-0.11
25-30	1637 (28.4)	1637 (28.4)	0.00	1638 (28.4)	5354 (26.5)	0.04
30-35	1299 (22.6)	1299 (22.6)	0.00	1300 (22.5)	3809 (18.9)	0.09
35-40	743 (12.9)	743 (12.9)	0.00	745 (12.9)	2007 (10.0)	0.09
>40	657 (11.4)	657 (11.4)	0.00	663 (11.5)	1661 (8.2)	0.10
Unknown	275 (4.8)	275 (4.8)	0.00	279 (4.8)	2099 (10.4)	-0.26
Time period						
6/01-30/2022	1864 (32.4)	1887 (32.8)	-0.01	1869 (32.4)	6856 (34.0)	-0.03
7/01-31/2022	2115 (36.8)	2091 (36.3)	0.01	2123 (36.8)	7161 (35.5)	0.03
8/01-31/2022	1267 (22.0)	1246 (21.7)	0.01	1270 (22.0)	4311 (21.4)	0.02
9/01-24/2022	508 (8.8)	530 (9.2)	-0.01	510 (8.8)	1839 (9.1)	0.01

Data are presented as mean [SD] for continuous measures, and n (%) for categorical measures.

Table 1: Patient characteristics and covariate balance before and after propensity matching (continued).

	After Propensity Matching			Before Propensity Matching		
	Nirmatrelvir-Ritonavir Cohort	Untreated Control Cohort	SMD	Nirmatrelvir-Ritonavir Cohort	Untreated Control Cohort	SMD
	N=5,754	N=5,754		N=5,772	N=20,167	
Myocardial Infarction	165 (2.9)	147 (2.6)	0.02	166 (2.9)	598 (3.0)	-0.01
Heart Failure	237 (4.1)	231 (4.0)	0.01	240 (4.2)	870 (4.3)	-0.01
Cerebrovascular Disease	241 (4.2)	220 (3.8)	0.02	242 (4.2)	822 (4.1)	0.01
Hemiplegia or Paraplegia	49 (0.9)	51 (0.9)	-0.00	50 (0.9)	186 (0.9)	-0.01
Peripheral Vascular Disease	314 (5.5)	289 (5.0)	0.02	315 (5.5)	754 (3.7)	0.07
Chronic Pulmonary Disease	1567 (27.2)	1456 (25.3)	0.04	1575 (27.3)	4275 (21.2)	0.14
Dementia	33 (0.6)	43 (0.7)	-0.02	33 (0.6)	170 (0.8)	-0.04
Hypertension	2337 (40.6)	2285 (39.7)	0.02	2351 (40.7)	5900 (29.3)	0.23
Diabetes without Chronic Complications	1055 (18.3)	1055 (18.3)	0.00	1067 (18.5)	2565 (12.7)	0.15
Diabetes with Chronic Complications	293 (5.1)	293 (5.1)	0.00	305 (5.3)	945 (4.7)	0.03
Renal Mild-Moderate-Advanced Disease (CKD stage 1-4)	255 (4.4)	252 (4.4)	0.00	258 (4.5)	917 (4.5)	-0.00
Renal Severe Disease (CKD stage 5 and ESRD)	20 (0.3)	21 (0.4)	0.00	20 (0.3)	226 (1.1)	-0.13
Mild Liver Disease	454 (7.9)	427 (7.4)	0.02	457 (7.9)	1154 (5.7)	0.08
Moderate to Severe Liver Disease	43 (0.7)	44 (0.8)	0.00	43 (0.7)	229 (1.1)	-0.05
Peptic Ulcer Disease	80 (1.4)	72 (1.3)	0.01	80 (1.4)	264 (1.3)	0.01
Rheumatic Disease	178 (3.1)	160 (2.8)	0.02	179 (3.1)	504 (2.5)	0.03
Malignancy	200 (3.5)	210 (3.6)	-0.01	201 (3.5)	461 (2.3)	0.07
Lymphoproliferative Disease	110 (1.9)	84 (1.5)	0.03	111 (1.9)	212 (1.1)	0.06
Metastatic Solid Tumor	79 (1.4)	70 (1.2)	0.01	79 (1.4)	163 (0.8)	0.05
HIV	17 (0.3)	19 (0.3)	-0.01	17 (0.3)	60 (0.3)	-0.00
Opportunistic Infection	362 (6.3)	350 (6.1)	0.01	365 (6.3)	1236 (6.1)	0.01
Solid Organ Transplant	16 (0.3)	14 (0.2)	0.01	16 (0.3)	114 (0.6)	-0.05

Data are presented as mean [SD] for continuous measures, and n (%) for categorical measures.
Abbreviations: SMD= standardized mean difference; IQR= interquartile range; BMI= body mass index; CKD= chronic kidney disease; ESRD= end-stage renal disease; HIV= Human Immunodeficiency Virus.

Table 2: The primary and secondary outcomes in the post-propensity score-matched cohorts.

Primary outcomes in post-propensity score-matched cohorts

	Nirmatrelvir-Ritonavir Cohort		Untreated Control Cohort			
	N (%)	95% CI*	N (%)	95% CI*	Difference in % with 95% CI*	*P-value*
Composite outcome within 30 days of enrollment	52 (0.9)	0.7, 1.2	122 (2.1)	1.8, 2.5	-1.2 (-1.7, -0.8)	< 0.01
All-cause hospitalization within 30 days of enrollment	50 (0.9)	0.6, 1.1	118 (2.1)	1.7, 2.5	-1.2 (-1.6, -0.7)	< 0.01
Mortality within 30 days of enrollment	2 (0.0)	0.0, 0.0	6 (0.1)	0.0, 0.2	-0.1 (-0.2, 0.0)	0.29

Secondary outcome in post-propensity score-matched cohort

	Nirmatrelvir-Ritonavir Cohort		Untreated Control Cohort			
	N (%)	95% CI*	N (%)	95% CI*	Difference in % with 95% CI*	*P-value*
Emergency visit within 30 days of index date	158 (2.7)	2.3, 3.2	213 (3.7)	3.2, 4.2	-1.0 (-1.6, -0.3)	< 0.01

Abbreviations: CI= Confidence Interval.

* The Clopper-Pearson method was used to calculate 95% confidence intervals (CI) for the outcome percentages using the R package (Exactci). CI for difference in paired proportions between the treatment and control cohorts.

Table 3: The primary composite outcome stratified by patient vaccination status*, age groups (<65, ≥ 65 years old), and immunocompromised status** among the propensity matched study cohort.

Primary outcome in the post-propensity-matched study cohort with subgroups

	Nirmatrelvir-Ritonavir Cohort		Untreated Control Cohort			
	N (%)	95% CI ***	N (%)	95% CI***	Difference in % with 95% CI***	*P-value*
Fully vaccinated N=4,836	11 (0.5)	0.2, 0.8	36 (1.5)	1.0, 2.1	-1.0 (-1.7, -0.4)	< 0.01
Not fully vaccinated N=4,160	41 (2.0)	1.4, 2.7	84 (4.0)	3.2, 5.0	-2.1 (-3.1, -1.0)	< 0.01
Immunocompromised N=484	6 (2.5)	0.9, 5.3	11 (4.5)	2.3, 8.0	-2.1 (-6.0, 1.7)	0.33
Not Immunocompromised N=10,582	39 (0.7)	0.5, 1.0	100 (1.9)	1.5, 2.3	-1.2 (-1.6, -0.7)	< 0.01
Age ≥ 65 N=3,972	26 (1.3)	0.9, 1.9	63 (3.2)	2.4, 4.0	-1.9 (-2.9, -0.9)	< 0.01
Age < 65 N=7,258	25 (0.7)	0.4, 1.0	55 (1.5)	1.1, 2.0	-0.8 (-1.3, -0.3)	<0.01

Abbreviations: CI= Confidence Interval

*This analysis included the patients with known vaccination status only.

**Immunocompromised status includes malignancy, lymphoproliferative disorders and hematopoietic stem cell transplants, solid organ transplants, and human immunodeficiency virus infected patients.

***The Clopper-Pearson method was used to calculate 95% confidence intervals for the outcome percentages using the R package (Exactci). CI for difference in paired proportions between the treatment and control cohorts.