Real-world use of nirmatrelvir–ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study

Neil R Aggarwal, Kyle C Molina*, Laurel E Beaty, Tellen D Bennett, Nichole E Carlson, David A Mayer, Jennifer L Peers, Seth Russell, Matthew K Wynia, Adit A Ginde*

Summary

Background Nirmatrelvir is a protease inhibitor with in-vitro activity against SARS-CoV-2, and ritonavir-boosted nirmatrelvir can reduce the risk of progression to severe COVID-19 among individuals at high risk infected with delta and early omicron variants. However, less is known about the effectiveness of nirmatrelvir–ritonavir during more recent BA.2, BA2.12.1, BA.4, and BA.5 omicron variant surges. We used our real-world data platform to evaluate the effect of nirmatrelvir–ritonavir treatment on 28-day hospitalisation, mortality, and emergency department visits among outpatients with early symptomatic COVID-19 during a SARS-CoV-2 omicron (BA.2, BA2.12.1, BA.4, and BA.5) predominant period in Colorado, USA.

Methods We did a propensity-matched, retrospective, observational cohort study of non-hospitalised adult patients infected with SARS-CoV-2 between March 26 and Aug 25, 2022, using records from a statewide health system in Colorado. We obtained data from the electronic health records of University of Colorado Health, the largest health system in Colorado, with 13 hospitals and 141 000 annual hospital admissions, and with numerous ambulatory sites and affiliated pharmacies around the state. Included patients had a positive SARS-CoV-2 test or nirmatrelvir–ritonavir medication order. Exclusion criteria were an order for or administration of other SARS-CoV-2 treatments within 10 days of a positive SARS-CoV-2 test, hospitalisation at the time of positive SARS-CoV-2 test, and positive SARS-CoV-2 test more than 10 days before a nirmatrelvir–ritonavir order. We propensity score matched patients treated with nirmatrelvir–ritonavir with untreated patients. The primary outcome was 28-day all-cause hospitalisation.

Findings Among 28 167 patients infected with SARS-CoV-2 between March 26 and Aug 25, 2022, 21 493 met the study inclusion criteria. 9881 patients received treatment with nirmatrelvir–ritonavir and 11 612 were untreated. Nirmatrelvir–ritonavir treatment was associated with reduced 28-day all-cause hospitalisation compared with no antiviral treatment (61 [0·9%] of 7168 patients *vs* 135 [1·4%] of 9361 patients, adjusted odds ratio (OR) 0·45 [95% CI 0·33–0·62]; p<0·0001). Nirmatrelvir–ritonavir treatment was also associated with reduced 28-day all-cause mortality (two [<0·1%] of 7168 patients *vs* 15 [0·2%] of 9361 patients; adjusted OR 0·15 [95% CI 0·03–0·50]; p=0·0010). Using subsequent emergency department visits as a surrogate for clinically significant relapse, we observed a decrease after nirmatrelvir–ritonavir treatment (283 [3·9%] of 7168 patients *vs* 437 [4·7%] of 9361 patients; adjusted OR 0·74 [95% CI 0·63–0·87]; p=0·0002).

Interpretation Real-world evidence reported during a BA.2, BA2.12.1, BA.4, and BA.5 omicron surge showed an association between nirmatrelvir–ritonavir treatment and reduced 28-day all-cause hospitalisation, all-cause mortality, and visits to the emergency department. With results that are among the first to suggest effectiveness of nirmatrelvir–ritonavir for non-hospitalised patients during an omicron period inclusive of BA.4 and BA.5 subvariants, these data support nirmatrelvir–ritonavir as an ongoing first-line treatment for adults acutely infected with SARS-CoV-2.

Funding US National Institutes of Health.

Lancet Infect Dis 2023

Published Online
February 10, 2023
https://doi.org/10.1016/S1473-3099(23)00011-7

See Online/Comment
https://doi.org/10.1016/S1473-3099(23)00056-7

*Contributed equally

Department of Medicine (N R Aggarwal MD, Prof M K Wynia MD), **Department of Biomedical Informatics** (T D Bennett MD, S Russell MS), **Department of Pediatrics** (T D Bennett, S Russell), **and Department of Emergency Medicine** (K C Molina PharmD, J L Peers BSN, Prof A A Ginde MD), **University of Colorado School of Medicine, Aurora, CO, USA; Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA** (K C Molina); **Department of Pharmacy, University of Colorado Hospital, Aurora, CO, USA** (K C Molina); **Department of Biostatistics and Informatics** (L E Beaty MS, Prof N E Carlson PhD, D A Mayer BS) **and Department of Health Systems Management and Policy** (Prof M K Wynia), **Colorado School of Public Health and Colorado Clinical and Translational Sciences Institute, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; Colorado Clinical and Translational Sciences Institute** (T D Bennett, S Russell), **University of Colorado Anschutz Medical Campus, Aurora, CO, USA; University of Colorado Center for Bioethics and Humanities, Aurora, CO, USA** (Prof M K Wynia)

Introduction

The global spread and impact of SARS-CoV-2 has highlighted the need for accessible therapeutics that improve patient outcomes and attenuate the effect of COVID-19 surges on health-care systems. Nirmatrelvir is an orally bioavailable protease inhibitor with activity against the main viral protease, M^{pro}, which is essential to SARS-CoV-2 viral replication.[1] In the EPIC-HR trial, treatment with ritonavir-boosted nirmatrelvir (Paxlovid; Pfizer Labs; NY, USA) resulted in a risk of progression to severe disease that was 89% lower than placebo among unvaccinated adults during the pre-delta and delta (B.1.617.2) pandemic phases.[2] On the basis of these results, in December, 2021, nirmatrelvir–ritonavir was granted US Food and Drug Administration (FDA) emergency use authorisation for the treatment of

Correspondence to:
Dr Neil R Aggarwal, Department of Medicine, University of Colorado School of Medicine, Aurora, CO 80045, USA
neil.aggarwal@cuanschutz.edu

Research in context

Evidence before this study

Nirmatrelvir–ritonavir, an oral antiviral for the treatment of outpatients with COVID-19 at high risk, has been shown to lower the risk of hospitalisation, thereby decreasing the burden of COVID-19 on the health-care system. We searched PubMed and medRxiv for studies published from database inception to Nov 1, 2022, using the search terms "Nirmatrelvir OR Paxlovid OR PF-07321332" AND "SARS-COV-2 OR COVID-19", without language restrictions. A major study that examined the safety and effectiveness of nirmatrelvir–ritonavir was the EPIC-HR trial, which showed that treatment initiation within 5 days of symptom onset was associated with an 88% reduced risk of COVID-19-related hospitalisation or death at 28 days. Real-world studies have shown similar benefits, albeit some studies have reported differential effects in selected subgroups, including attenuated effectiveness in those younger than 65 years. Furthermore, these studies were done before the emergence of SARS-CoV-2 omicron variants BA.4 and BA.5.

Added value of this study

To our knowledge, the current study is one of the first to examine the effectiveness of nirmatrelvir–ritonavir in non-hospitalised patients during the omicron period of the COVID-19 pandemic, which includes the BA.4 and BA.5 subvariants. Compared with propensity-matched untreated patients, treatment with nirmatrelvir–ritonavir was associated with a significantly lower risk of all-cause and COVID-19-specific hospitalisation, a finding consistent across most clinically important subgroups. Treatment with nirmatrelvir–ritonavir was also associated with significantly lower all-cause mortality and lower rates of post-treatment emergency department visits, indicating a low likelihood of clinically significant relapse.

Implications of all the available evidence

Current international guidelines recommend nirmatrelvir–ritonavir treatment for patients with non-severe COVID-19 who are at high risk of hospitalisation or death. Our study of real-world use of nirmatrelvir–ritonavir in outpatients at high risk extends previous data by showing strong evidence of nirmatrelvir–ritonavir benefit during the omicron BA.4 and BA.5 SARS-CoV-2 subvariant period and for vaccinated patients and for those younger than 65 years.

mild-to-moderate COVID-19 in adult and paediatric patients who were at high risk for progression to severe COVID-19, including hospitalisation or death.[3]

Since the authorisation of nirmatrelvir–ritonavir, the landscape of the COVID-19 pandemic has evolved. Omicron lineage variants of SARS-CoV-2 that show high transmissibility and immune evasion, yet are associated with decreased disease severity, have supplanted previous variants.[4] Although spike protein mutations present in emergent variants have continuously impacted important COVID-19 therapeutics (eg, monoclonal antibodies), nirmatrelvir–ritonavir, which targets M^{pro}, has thus far maintained in-vitro activity against emergent variants. Real-world observations have postulated a nirmatrelvir–ritonavir rebound effect, whereby patients might have an increase in viral load or recurrent symptoms after treatment.[5,6] However, the incidence of clinically significant relapse in patients treated with nirmatrelvir–ritonavir leading to emergency department visits or hospitalisation is unknown. Vaccination against COVID-19 has become widespread since investigation of the unvaccinated population in the EPIC-HR trial.[2] Several observational studies have shown the benefits of nirmatrelvir–ritonavir treatment, primarily during the delta-variant and early omicron-variant phases of COVID-19.[7–11] However, clinical data regarding the effectiveness of nirmatrelvir–ritonavir against more recent omicron variants, including BA.4 and BA.5, are lacking.

Given the epidemiological shift in circulating variants, a suggestion of a rebound phenomenon, and extensive vaccination of individuals at high risk, real-world data are crucial to evaluate the impact of nirmatrelvir–ritonavir and other therapies targeting COVID-19 to inform ongoing policy and practice decisions. To provide additional data on nirmatrelvir–ritonavir effectiveness against more recent omicron subvariants of SARS-CoV-2, we used our real-world data platform to evaluate the effect of nirmatrelvir–ritonavir treatment on 28-day hospitalisation, mortality, and emergency department visits among outpatients with early symptomatic COVID-19 during a SARS-CoV-2 omicron (BA.2, BA2.12.1, BA.4, and BA.5) predominant period in Colorado, USA.

Methods

Study design and participants

We did a propensity-matched, retrospective, observational cohort study, which was a collaboration between University of Colorado researchers, University of Colorado Health leaders, and the Colorado Department of Public Health and Environment.[12–14] The study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent. We obtained data from the electronic health records (Epic; Verona, WI, USA) of University of Colorado Health, the largest health system in Colorado, with 13 hospitals and 141 000 annual hospital admissions, with numerous ambulatory sites and affiliated pharmacies around the state, using Health Data Compass, an enterprise-wide data warehouse. Electronic health record data were merged with statewide data on vaccination status from the Colorado Comprehensive Immunization

Information System and mortality from Colorado Vital Records. This analysis conforms to STROBE reporting guidance (appendix 1 pp 3–4).

As described in the prespecified statistical analysis plan (appendix 2 pp 3–4), we included all patients diagnosed with SARS-CoV-2 infection identified using electronic health record-based SARS-CoV-2 positive test date (either PCR or antigen test) or nirmatrelvir–ritonavir medication order date if a SARS-CoV-2 test result was unavailable. Patients were included if their positive test date was between March 26 and Aug 25, 2022, which allowed for a minimum of 28 days of follow-up (n=28 167; appendix 1 p 5). Until March 11, 2022, patients treated with nirmatrelvir–ritonavir accounted for less than 10% of the available patients identified through the University of Colorado Health electronic health records, and starting on March 26, they comprised at least 25% of these available patients. To avoid sparse data and to ensure proper propensity matching on time, we implemented a cohort inclusion date of March 26, 2022. Nirmatrelvir–ritonavir was readily available during this period, and the dominant SARS-CoV-2 variant was omicron. We did not exclude patients who did not have a recorded emergency use authorisation-qualifying condition based on electronic health record data, as all eligibility criteria were not consistently available. The main exclusion criteria were as follows: order or administration of molnupiravir, or administration of any other SARS-CoV-2 monoclonal antibody or antiviral (including bebtelovimab, sotrovimab, tixagevimab–cilgavimab [within 10 days of SARS-CoV-2 positive test date], or outpatient remdesivir; n=5676), SARS-CoV-2 positive test during hospital admission, or being in hospital at the time of nirmatrelvir–ritonavir order, or discharge on the same date of nirmatrelvir–ritonavir order (n=993), or a positive SARS-CoV-2 test more than 10 days before the nirmatrelvir–ritonavir medication order date (n=5). We retained patients who were hospitalised or died later on the same day as their observed SARS-CoV-2 positive test, temporally after their first positive test given the common use of home self-testing during the study period.

Participant sex was defined by legal sex in the electronic health record, as reported by the patient. Options provided were male or female.

Procedures

The decision to seek antiviral treatment was made by patients and clinicians based on clinical guidance, which mirrored that of National Institutes of Health COVID-19 guidelines.[15] Briefly, nirmatrelvir–ritonavir was the preferred therapy for non-hospitalised adults with COVID-19 at high risk within 5 days of symptom onset and without contraindications due to drug–drug interactions or comorbidities. Nirmatrelvir–ritonavir treatment comprised 300 mg nirmatrelvir (150 mg with moderate renal impairment) and 100 mg ritonavir orally, twice daily, for 5 days.

Notably, most patients treated with nirmatrelvir–ritonavir did not have a SARS-CoV-2 positive test date in the health system electronic health records. Because a prescription of nirmatrelvir–ritonavir requires a positive SARS-CoV-2 test, we assumed that testing occurred at home or at a location outside the health system for these patients. As many patients received antiviral treatment the same or next day after a positive SARS-CoV-2 test, for analytic purposes we used a SARS-CoV-2 positivity test date (the index date) of one day before the recorded nirmatrelvir–ritonavir order date for the primary analysis.

See Online for appendix 1

See Online for appendix 2

To achieve balance on potential confounders, we used nearest neighbour propensity matching with logistic regression with treatment status as the outcome.[16,17] We attempted to achieve a ratio of up to 2:1; however, given the scarcity of untreated patients (appendix 1 pp 11–13), we achieved a matching ratio of 1·31:1 treated to untreated patients, with a total matched cohort size of 16 529, consistent with the approach recommended by Austin to optimise precision while minimising bias.[18] The propensity model included binary age (<65 years *vs* ≥65 years), sex, binary race and ethnicity (non-Hispanic White *vs* other race or ethnicity), insurance status, immunocompromised status, obesity status, number of comorbid conditions other than immunocompromised status and obesity, number of vaccinations at the time of infection, and categorical week of SARS-CoV-2 positive test date. We removed patients treated with nirmatrelvir–ritonavir because of missing covariate data and used the recommended caliper of 0·2, which removed an additional 3043 patients (1892 patients treated with nirmatrelvir–ritonavir; appendix 1 pp 8–9).[19] Variables with a remaining standardised mean difference above 0·1 were adjusted for in all outcome models to account for residual imbalance.[20] A comparison of the unmatched sample to the matched sample is provided in appendix 1 (pp 12–13).

Variable definitions

Hospitalisation was defined as any inpatient or observation encounter documented in the electronic health record. We selected the first hospitalisation that occurred the same day, or any day after, a SARS-CoV-2 positive test for untreated patients, or after the order date for nirmatrelvir–ritonavir for treated patients. Emergency department visits were defined as any visit to the emergency department, with or without an associated inpatient or observation encounter. For patients treated with nirmatrelvir–ritonavir, we selected the first emergency department visit that occurred at least one day after the nirmatrelvir–ritonavir order date, given that nirmatrelvir–ritonavir treatment was often prescribed at the initial emergency department visit (and thus should not be considered a treatment failure outcome). We defined COVID-19 disease severity as the maximum level of respiratory support received in the following order from lowest to highest severity: no supplemental oxygen,

standard (nasal cannula or face mask) oxygen, high-flow nasal cannula or non-invasive ventilation, and invasive mechanical ventilation.[21] In-hospital mortality was the highest level of disease severity.

The covariates of interest included treatment status, categorical age in years, sex, race and ethnicity, insurance status, binary obesity status (not obese *vs* obese), immunocompromised status, number of additional comorbid conditions, three-level vaccination status (none, one, or two), and omicron subvariant period (BA.4 or BA.5). Electronic heath record evidence of comorbid conditions (obesity, hypertension, cardiovascular disease, diabetes, pulmonary disease, and liver disease) was based on the Charlson and Elixhauser Comorbidity Indices, and immunocompromised status was coded as reported previously (appendix 1 p 10).[14] The number of comorbid conditions was calculated as the sum of these specific conditions, with obesity and immunocompromised status kept as separate comorbid conditions in the analysis. Vaccination status was further categorised by the number of vaccinations (none, one, two, or three or more) administered before the observed or imputed SARS-CoV-2 positive test date. Based on statewide virus strain data, we considered patients with an observed or imputed SARS-CoV-2 positive test on or after June 19, 2022, to be in the omicron BA.4 or BA.5 period, given that the statewide proportion of BA.4 or BA.5 was above 50% by that date, and rose to above 90% by July 10, 2022 (appendix 1 p 6).[22]

Outcomes

The primary outcome was all-cause hospitalisation within 28 days of a positive SARS-CoV-2 test, based on the observed or imputed test date. As a secondary outcome, we defined COVID-19-related 28-day hospitalisation as the presence of any of the following: COVID-19 International Classification of Diseases-10 code (U07·1, J12·82, M35·81, Z20·822, or M35·89), administration of inpatient remdesivir, or use of any supplemental oxygen. Other secondary outcomes included 28-day all-cause mortality, hospital length of stay and odds of intensive care unit admission in the hospitalised subset, and 28-day all-cause emergency department visits. In the hospitalised subset, exploratory outcomes included disease severity based on the maximum level of respiratory support and in-hospital mortality.

Statistical analysis

We used Firth's logistic regression to assess the association between treatment and 28-day hospitalisation, 28-day mortality, and 28-day emergency department visits, and we considered a two-sided p value of less than 0·05 to be statistically significant without adjustment for multiple comparisons. Firth's logistic regression (R package logistf version 1.24) addresses estimation issues related to low event rates and complete separation.[23–25] All models were adjusted for age, sex, race and ethnicity, insurance status, obesity status, immunocompromised status, number of additional comorbid conditions, number of vaccinations, and omicron subvariant. We fit cumulative incidence plots to estimate the time from SARS-CoV-2 positive test to all-cause hospitalisation and all-cause emergency department visits. Care should be used in interpreting these curves because of the frequent use of rapid antigen home testing before a health-care encounter for an electronic health record-tracked SARS-CoV-2 test result or treatment. For the 28-day hospitalisation secondary outcomes, we fit an adjusted logistic regression to assess the association between treatment and the odds of being transferred to the intensive care unit. Additionally, to evaluate the difference in hospital length of stay, we fit an adjusted negative binomial regression and reported adjusted incidence risk ratios (RRs) to account for overdispersion in the outcome. A likelihood ratio test was done to compare the adjusted Poisson model to the adjusted negative binomial model, and a test of overdispersion found estimated dispersion in the Poisson model was 5·6 ($p<0·0001$).[26] Because of the small number of hospitalised participants, we present only descriptive statistics for respiratory disease severity and intensive care unit length of stay.

We estimated adjusted treatment effects for eight subgroups of interest by fitting interaction models that were also adjusted for all variables of interest. The subgroups of interest included binary age (<65 years *vs* ≥65 years), binary obesity status (not obese *vs* obese), and three-level immunocompromised status (not immunocompromised *vs* mild immunocompromised *vs* moderate–severe immunocompromised), binary number of comorbidities (0–1 *vs* ≥2), binary vaccination status (0–2 *vs* ≥3), three-level vaccination status (0 *vs* 1–2 *vs* ≥3), and omicron subvariant period (before BA.4 and BA.5 and during BA.4 and BA.5).

We did several sensitivity analyses that repeated the primary analysis using different assumptions with subsequent propensity matching. For the first sensitivity analysis, we only selected patients with electronic health record-derived data on emergency use authorisation-qualifying conditions (appendix 1 pp 14–16). We implemented a second method of determining SARS-CoV-2 positive date for patients treated with nirmatrelvir–ritonavir by imputing a 3-day difference between treatment initiation and assumed SARS-CoV-2 positive date to account for a fixed delay (eg, over a weekend) between a home test positive result and prescribed treatment (appendix 1 pp 17–20). Additionally, we did four post-hoc sensitivity analyses. First, because nirmatrelvir–ritonavir is contraindicated in patients with severe renal or liver dysfunction, patients who are more well in general might be treated with nirmatrelvir–ritonavir, potentially biasing in favour of a beneficial treatment effect. We removed patients with renal disease

and severe liver disease (appendix 1 pp 20–21). As there was a high proportion of SARS-CoV-2 test date missingness among patients treated with nirmatrelvir–ritonavir, we also did a sensitivity analysis of only those with an observed test date (appendix 1 pp 21–23). As a test to the assumption that patients who were hospitalised on the same day as a positive test or nirmatrelvir–ritonavir order had time to receive benefit from the treatment, we did an analysis that excluded those who were hospitalised on the same calendar day as a positive SARS-CoV-2 test or nirmatrelvir–ritonavir order (appendix 1 pp 23–25). Finally, we evaluated the primary cohort using a 1:1 propensity matching ratio that reduced the potential for bias (appendix 1 pp 25–26).[16]

All statistical analyses were done using R Statistical Software (version 3.6.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among 28 167 patients infected with SARS-CoV-2 between March 26 and Aug 25, 2022, 21 493 met the study inclusion criteria. 9881 patients received treatment with nirmatrelvir–ritonavir and 11 612 were untreated (appendix 1 p 5), with baseline characteristics showing some important differences, including older age, higher rate of Medicare insurance, and more participants with two or more comorbidities in the nirmatrelvir–ritonavir group than the untreated group (appendix 1 pp 11–13). We observed substantial overlap in propensity distributions before propensity matching (untreated mean 0·405 [SD 0·165]; treated mean 0·530 [0·164]). Propensity score matching resulted in 16 529 patients (7168 treated with nirmatrelvir–ritonavir, 9361 untreated) for the primary analysis, with similar standardised mean differences of variables for most prognostic factors that were measured (appendix 1 p 9). The covariates with a standardised mean difference higher than 0·1 were age, immunocompromised status, number of comorbid conditions, and week. The characteristics of the primary propensity-matched cohort are in table 1. The cohort treated with nirmatrelvir–ritonavir generally reflected the characteristics of patients at high risk for progression to severe COVID-19. Among the patients treated with nirmatrelvir–ritonavir, 2298 (32·1%) were aged 65 years or older, 1015 (14·1%) were Hispanic or non-Hispanic Black, 1924 (26·8%) were obese, 1768 (24·6%) were immunocompromised, and 2186 (30·5%) had two or more other comorbid conditions.

Treatment with nirmatrelvir–ritonavir was associated with significantly lower odds of 28-day all cause hospitalisation compared with no antiviral treatment (61 [0·9%] of 7168 patients *vs* 135 [1·4%] of 9361 patients, adjusted odds ratio (OR) 0·45 [95% CI 0·33–0·62]; p<0·0001; table 2; figure 1). Using our definition, 156 (79·6%) of 196 hospitalisations were designated as COVID-19-related and, among this subset, the odds of 28-day hospitalisation in patients treated with nirmatrelvir–ritonavir compared with no antiviral treatment were similar to the primary all-cause hospitalisation outcome (47 [0·7%] of 7168 patients *vs* 109 [1·2%] of 9361 patients; adjusted OR 0·40 [95% CI 0·28–0·57]; p<0·0001).

	Nirmatrelvir–ritonavir group (n=7168)	Untreated group (n=9361)
Age, years*		
18–44	3288 (45·9%)	5964 (63·7%)
45–64	1582 (22·1%)	1442 (15·4%)
≥65	2298 (32·1%)	1955 (20·9%)
Sex		
Female	4202 (58·6%)	5462 (58·3%)
Male	2966 (41·4%)	3899 (41·7%)
Race and ethnicity		
Non-Hispanic White	5826 (81·3%)	7365 (78·7%)
Hispanic	768 (10·7%)	1106 (11·8%)
Non-Hispanic Black	247 (3·4%)	447 (4·8%)
Other	327 (4·6%)	443 (4·7%)
Insurance status*†		
Private or commercial	4349 (60·7%)	6414 (68·5%)
Medicare	2176 (30·4%)	1911 (20·4%)
Medicaid	401 (5·6%)	679 (7·3%)
None or uninsured	51 (0·7%)	91 (1·0%)
Other or unknown	191 (2·7%)	266 (2·8%)
Immunocompromised*		
Mild	923 (12·9%)	724 (7·7%)
Moderate or severe	845 (11·8%)	736 (7·9%)
Obese*	1924 (26·8%)	1793 (19·2%)
Number of comorbid conditions		
One	2192 (30·6%)	2519 (26·9%)
Two or more	2186 (30·5%)	1931 (20·6%)
Diabetes	1077 (15·0%)	897 (9·6%)
Cardiovascular disease	1093 (15·2%)	1079 (11·5%)
Pulmonary disease	2028 (28·3%)	2065 (22·1%)
Renal disease	421 (5·9%)	488 (5·2%)
Hypertension	2690 (37·5%)	2550 (27·2%)
Liver disease		
Mild	614 (8·6%)	564 (6·0%)
Severe	33 (0·5%)	39 (0·4%)
Number of vaccinations before positive SARS-CoV-2 test date*		
0	1460 (20·4%)	2036 (21·7%)
1	292 (4·1%)	393 (4·2%)
2	1062 (14·8%)	1537 (16·4%)
≥3	4354 (60·7%)	5395 (57·6%)

*Variables used in the propensity matching, along with cohort week of positive SARS-CoV-2 test date (not listed). †Private or commercial insurance and Medicare were collapsed for multivariable models due to collinearity between age and Medicare insurance.

Table 1: **Baseline characteristics**

	Nirmatrelvir–ritonavir group	Untreated group	Adjusted odds ratio or adjusted risk ratio (95% CI)	p value
Overall sample size*				
All-cause 28-day hospitalisation	61 (0·9%)	135 (1·4%)	0·45 (0·33–0·62)	<0·0001
COVID-19-related 28-day hospitalisation†	47 (0·7%)	109 (1·2%)	0·40 (0·28–0·57)	<0·0001
All-cause 28-day emergency department visit	283 (3·9%)	437 (4·7%)	0·74 (0·63–0·87)	0·0002
All-cause 28-day mortality	2 (<0·1%)	15 (0·2%)	0·15 (0·03–0·50)	0·0010
Hospitalised sample size†				
Hospital length of stay, days‡	3·4 (3·9)	5·2 (7·9)	0·70 (0·53–0·93)	0·013
Intensive care unit visit during hospitalisation	3 (4·9%)	20 (14·8%)	0·35 (0·09–1·03)	0·058

Data are n (%) or mean (SD). *n=7168 for the nirmatrelvir–ritonavir group and n=9361 for the untreated group. †n=61 for the nirmatrelvir–ritonavir group and n=135 for the untreated group. ‡Negative binomial models presented as adjusted risk ratios with 95% CIs.

Table 2: **Primary and secondary outcomes for the primary matched cohort**

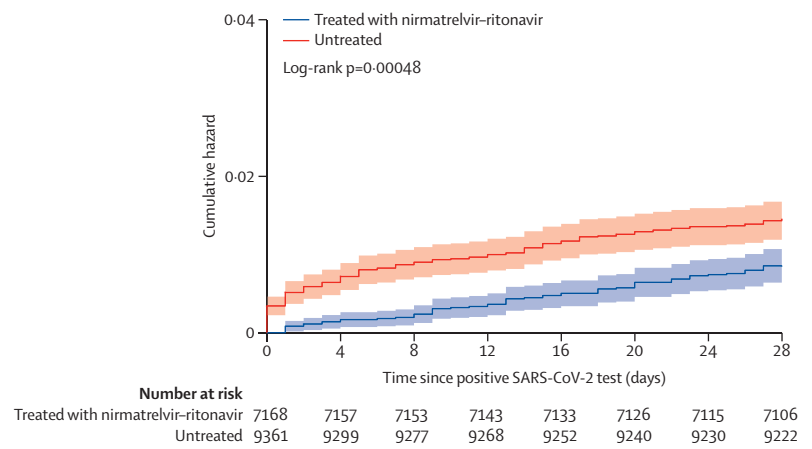

Figure 1: **Cumulative incidence plots for all-cause hospitalisation to day 28 by treatment status**

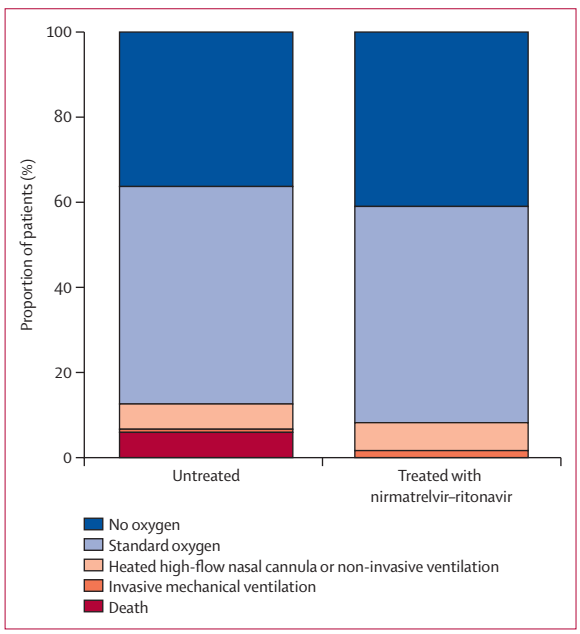

Figure 2: **Severity of all-cause hospitalisation to day 28**
Total sample size of the hospitalised subset was 196 (61 patients in the nirmatrelvir–ritonavir group and 135 in the untreated group).

Treatment with nirmatrelvir–ritonavir was associated with significantly lower 28-day all-cause mortality compared with untreated patients (two [<0·1%] of 7168 patients *vs* 15 [0·2%] of 9361 patients; adjusted OR 0·15 [95% CI 0·03–0·50]; p=0·0010; table 2). Additionally, among the subset of hospitalised patients in our cohort, nirmatrelvir–ritonavir treatment was associated with a shorter mean hospital length of stay compared with the untreated group (3·4 days [SD 3·9] *vs* 5·2 days [7·9]; adjusted RR 0·70 [95% CI 0·53–0·93]; p=0·013). The observed rate of high-flow nasal oxygen use, need for invasive mechanical ventilation, or occurrence of death was lower in patients treated with nirmatrelvir–ritonavir compared with untreated patients (five [8·2%] of 61 patients *vs* 17 [12·6%] of 135 patients), although inferential statistics could not be performed because of low event rates (figure 2).

We used emergency department visits occurring after initial diagnosis and treatment decision as a surrogate for clinically important relapse after nirmatrelvir–ritonavir treatment because we could not track COVID-19-related symptoms that did not require an emergency department visit in our electronic health record-derived cohort. The time to emergency department visit from positive SARS-CoV-2 test did not visually show a positive inflection in emergency department visits after the 5-day nirmatrelvir–ritonavir treatment completion, which might be expected with a severe relapse effect (appendix 1 p 7). Overall, the nirmatrelvir–ritonavir group had lower odds of an emergency department visit within 28 days compared with untreated controls (283 [3·9%] of 7168 patients *vs* 437 [4·7%] of 9361 patients; adjusted OR 0·74 [95% CI 0·63–0·87]; p=0·0002; table 2).

Among subgroups, treatment effects were similar for those who were younger than 65 years and those aged 65 years and older ($p_{interaction}$=0·25), immunocompromised status ($p_{interaction}$=0·80), obesity ($p_{interaction}$=0·86), and vaccination status (one or two vaccinations $p_{interaction}$=0·74; three or more vaccinations $p_{interaction}$=0·99; figure 3).

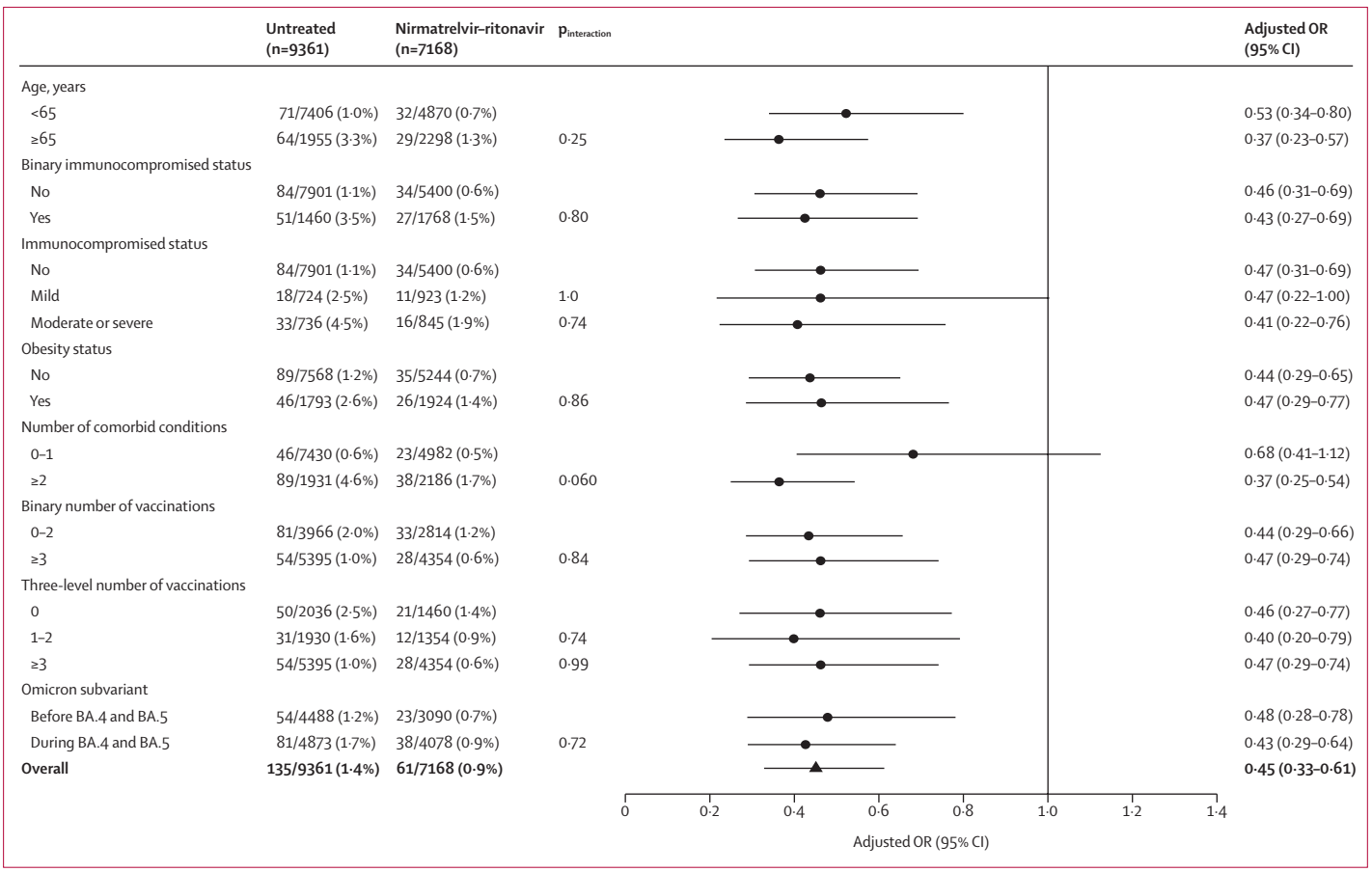

Figure 3: **Forest plot for subgroup analysis of outpatients infected with omicron**
The primary outcome for all subgroup analyses was 28-day all-cause hospitalisation, and all subgroup models were adjusted for all variables in the primary analysis. Raw counts and proportions are presented, along with the adjusted OR (95% CI) for the treatment effect in the subgroup of interest. OR=odds ratio.

Notably, the treatment effect was similar during omicron predominance before emergence of the BA.4 and BA.5 strains (ie, BA.2 and BA.2.12.1) and during the period of BA.4 and BA.5 predominance ($p_{interaction}$=0·72), despite apparent differences in hospitalisation rates among untreated patients during predominant BA.2 and BA.2.12.1 (54 [1·2%] of 4488 patients) and predominant BA.4 and BA.5 (81 [1·7%] of 4873 patients) periods. Treatment effect differed only on the basis of the number of comorbid conditions, as patients with zero to one other comorbid condition might have had an attenuated effect of nirmatrelvir–ritonavir treatment on 28-day all-cause hospitalisation compared with patients with two or more other comorbid conditions (adjusted OR 0·68 [95% CI 0·41–1·12] *vs* 0·37 [95% CI 0·25–0·54]; $p_{interaction}$=0·060; figure 3).

All prespecified and post-hoc sensitivity analyses were generally consistent with the primary analysis (table 3; appendix 1 pp 14–26), including a cohort derived from 1:1 propensity matching (adjusted OR 0·44 [95% CI 0·32–0·59]). Excluding patients hospitalised on the same calendar day as their observed SARS-CoV-2 test (untreated group) or nirmatrelvir–ritonavir order (nirmatrelvir–ritonavir group) resulted in a point estimate (adjusted OR 0·58 [95% CI 0·42–0·81]) within confidence intervals of the primary cohort analysis (95% CI 0·33–0·62), suggesting a similar treatment effect.

Discussion

During a SARS-CoV-2 omicron predominant phase that included BA.4 and BA.5 in Colorado, USA, nirmatrelvir–ritonavir treatment was associated with a reduced incidence of both 28-day all-cause hospitalisation, the primary outcome, as well as 28-day COVID-19-related hospitalisation, compared with no treatment. Nirmatrelvir–ritonavir administration to outpatients at high risk was also associated with reduced COVID-19 illness severity, as evidenced by reductions in all-cause 28-day mortality and intensive care unit admission. Waning COVID-19 severity, increased vaccination rates, varying time to treatment initiation after symptom onset, and presumed lower adherence to the prescribed five-day regimen in a real-world study might explain the reduced nirmatrelvir–ritonavir effectiveness in our study compared with the pivotal EPIC-HR trial;[2] despite these

	Nirmatrelvir–ritonavir group	Untreated group	Adjusted odds ratio (95% CI)	p value
Primary matched	61/7168 (0·9%)	135/9361 (1·4%)	0·45 (0·33–0·62)	<0·0001
Emergency use authorisation-qualifying condition only	54/6190 (0·9%)	132/7091 (1·9%)	0·40 (0·29–0·55)	<0·0001
SARS-CoV-2 positive test date imputation method 2	57/7231 (0·8%)	134/9407 (1·4%)	0·42 (0·30–0·57)	<0·0001
Emergency use authorisation-qualifying condition and participants without renal disease or severe liver disease	43/5692 (0·8%)	93/6574 (1·4%)	0·46 (0·31–0·66)	<0·0001
Cohort with observed SARS-CoV-2 test date	24/1470 (1·6%)	69/2933(2·4%)	0·68 (0·42–1·07)	0·096
Cohort excluding same day hospitalisation	59/7079 (0·8%)	103/9220 (1·1%)	0·58 (0·42–0·81)	0·0011
1:1 propensity-matched primary cohort	61/7168 (0·9%)	125/7168 (1·7%)	0·44 (0·32–0·59)	<0·0001

All sensitivity analyses were fit using Firth's bias-reducing logistic regression, with 28-day all-cause hospitalisation as the outcome, and were adjusted for all covariates in the primary analysis.

Table 3: **Primary and sensitivity analyses for all-cause hospitalisation at 28 days**

factors, nirmatrelvir–ritonavir remained significantly associated with benefits among patients at high risk and among clinically relevant subgroups infected with SARS-CoV-2. Additionally, we believe our data to be among the first to support the effectiveness of nirmatrelvir–ritonavir treatment among outpatients at high risk during a BA.4 and BA.5 omicron subvariant predominant period.

Nirmatrelvir–ritonavir treatment was associated with fewer emergency department visits in the 28 days following administration compared with matched, untreated patients, a finding that expands upon a single-arm study by Malden and colleagues,[6] who found that emergency department visits or hospitalisations occurred with less than 1% frequency in the 5–15 days after nirmatrelvir–ritonavir treatment.[6] Although our data cannot be used to estimate the overall frequency of rebound episodes among treated and untreated patients, they provide some reassurance that clinically significant relapse requiring emergency department visitation does not occur with increased frequency among patients treated with nirmatrelvir–ritonavir.

Our findings support the observations that nirmatrelvir–ritonavir can neutralise omicron variants in vitro and effectively treat outpatients at high risk and inpatients with lower-severity disease.[7,8,27–29] In our cohort, we observed that nirmatrelvir–ritonavir might have been beneficial in patients both older and younger than 65 years, as did Zhou and colleagues[30] and Shah and colleagues,[31] supporting the generalisability of our results. Notably, a study by Arbel and colleagues found that only COVID-19-positive outpatients at high risk aged 65 years or older had reduced hospitalisation after nirmatrelvir–ritonavir treatment, with an adjusted hazard ratio of 0·21, in contrast to those younger than 65 years, who appeared to derive no benefit.[7] This discrepancy might be due to differences in setting, including thresholds for hospitalisation in younger patients, population differences, the emergence of BA.4 and BA.5, or other unmeasured factors.

This study has several limitations. Hospitalisation data were collected only within a single health system that has relatively low representation with regard to race and ethnicity but good representation of urban and rural settings at academic and community hospitals, and is the largest health system in the state. Furthermore, symptom duration was not available in our dataset so we are unable to confirm symptom onset within 5 days among patients treated with nirmatrelvir–ritonavir required by the FDA emergency use authorisation. Given the use of single health system electronic health records, it is also possible that treatment, as well as most outcomes, might have occurred elsewhere, leading to misclassification; however, because we have statewide data, the mortality outcome is comprehensive. Although we anticipate similar propensity for hospitalisation within the health system between untreated patients and patients treated with nirmatrelvir–ritonavir, if untreated patients were more likely to be hospitalised outside this health system, or if patients prescribed nirmatrelvir–ritonavir did not fill the prescription or took less than all 5 days of prescribed treatment, our results might be biased towards the null. Although propensity matching was effective across multiple measured variables, residual confounding and unmeasured confounders might remain.

SARS-CoV-2 test result missingness was high and unbalanced in this cohort, with a large proportion of patients treated with nirmatrelvir–ritonavir treated without laboratory test results in our health system. At the present juncture in the pandemic, we speculate this missingness was high because symptomatic individuals were doing rapid SARS-CoV-2 antigen tests at home and reporting those results to providers, who then prescribed nirmatrelvir–ritonavir or other available antiviral therapies. As such, for patients in the nirmatrelvir–ritonavir group, we imputed the test date based on the nirmatrelvir–ritonavir order date combined with knowledge of local practice patterns, and then executed a sensitivity analysis using a fixed 3-day difference between nirmatrelvir–ritonavir treatment and positive test date. The post-hoc sensitivity analysis derived from a cohort of only patients with an observed SARS-CoV-2 postitive test date was 70% smaller than the primary cohort, and the point estimate for a nirmatrelvir–ritonavir association with reduced 28-day hospitalisation

did not reach statistical significance. Unlike in our previous analyses we did not exclude hospitalisations on the date of a known positive test[13] because of changes in testing practices. These approaches might introduce bias in the early days of the time to event analysis and, as such, cumulative incidence curves should be interpreted with caution. However, the post-hoc sensitivity analysis that excluded patients hospitalised the same day as their positive test or nirmatrelvir–ritonavir order had a slightly higher point estimate, but overall revealed statistically similar results to the primary cohort analysis.

In conclusion, this study of real-world data showed that nirmatrelvir–ritonavir treatment was associated with substantially reduced 28-day hospitalisation and all-cause 28-day mortality among outpatients at high risk with COVID-19 during an omicron phase, importantly inclusive of a BA.4 and BA.5 period. Using emergency department visits as a surrogate for clinically significant relapse after initial evaluation and treatment, we observed a lower emergency department visit rate in patients treated with nirmatrelvir–ritonavir compared with untreated patients, and it is reassuring that rebound symptoms after nirmatrelvir–ritonavir treatment appear to be rarely severe. With results that are among the first to suggest effectiveness of nirmatrelvir–ritonavir for non-hospitalised patients during an omicron period inclusive of BA.4 and BA.5 subvariants, these data support nirmatrelvir–ritonavir as an ongoing first-line treatment for adults acutely infected with SARS-CoV-2.

Contributors

AAG conceived the study and obtained the funding. NRA, KCM, LEB, NEC, and AAG designed the study. LEB and NEC analysed the data. LEB, TDB, NEC, DAM, and SR accessed and verified the data. NRA and KCM drafted the original version of the manuscript. All authors had full access to the data, reviewed the manuscript, contributed to data interpretation, approved the final version, and accept responsibility for the decision to submit for publication.

Declaration of interests

NRA reports grants from the US National Institutes of Health (NIH), during the conduct of the study. KCM reports grants from the National Center for Advancing Translational Sciences (NCATS), during the conduct of the study, and grants from the National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung, and Blood Institute (NHLBI), outside of the submitted work. TDB reports grants from the NCATS, during the conduct of the study, and grants from the NICHD and NHLBI, outside of the submitted work. NEC reports grants from the US NIH, during the conduct of the study. AAG reports grants from the US NIH during the conduct of the study, grants from the US Centers for Disease Control, the US Department of Defense, AbbVie, and Faron Pharmaceuticals, and participation on an NIH data safety monitoring board, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Deidentified participant data and a data dictionary defining each field in the set, as well as a statistical analysis plan, will be made available to others with publication upon provision of a signed data access agreement and approval by the project steering committee via communication with the corresponding author (neil.aggarwal@cuanschutz.edu).

Acknowledgments

This study was funded by the National Center for Advancing Translational Sciences of the National Institutes of Health, and supported by the Health Data Compass Data Warehouse project.

References

1 Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021; **374:** 1586–93.

2 Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med* 2022; **386:** 1397–408.

3 US Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. https://www.fda.gov/media/155050/download (accessed Nov 1, 2022).

4 Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022; **399:** 1303–12.

5 Coulson JM, Adams A, Gray LA, Evans A. COVID-19 "rebound" associated with nirmatrelvir/ritonavir pre-hospital therapy. *J Infect* 2022; **85:** 436–80.

6 Malden DE, Hong V, Lewin BJ, et al. Hospitalization and emergency department encounters for COVID-19 after paxlovid treatment—California, December 2021–May 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 830–33.

7 Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe COVID-19 outcomes during the omicron surge. *N Engl J Med* 2022; **387:** 790–98.

8 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. *Lancet Infect Dis* 2022; **22:** 1681–93.

9 Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of paxlovid in reducing severe COVID-19 and mortality in high risk patients. *Clin Infect Dis* 2022; published online June 2. https://doi.org/10.1093/cid/ciac443.

10 Razonable RR, O'Horo JC, Hanson SN, et al. Comparable outcomes for bebtelovimab and ritonavir-boosted nirmatrelvir treatment in high-risk patients with coronavirus disease-2019 during severe acute respiratory syndrome coronavirus 2 BA.2 omicron epoch. *J Infect Dis* 2022; **226:** 1683–87.

11 Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 and hospitalization in a large US health system. *medRxiv* 2022; published online June 17. https://doi.org/10.1101/2022.06.14.22276393/ (preprint).

12 Wynia MK, Beaty LE, Bennett TD, et al. Real-world evidence of neutralizing monoclonal antibodies for preventing hospitalization and mortality in COVID-19 outpatients. *Chest* 2022; published online Oct 27. https://doi.org/10.1016/j.chest.2022.10.020.

13 Aggarwal NR, Beaty LE, Bennett TD, et al. Real-world evidence of the neutralizing monoclonal antibody sotrovimab for preventing hospitalization and mortality in COVID-19 outpatients. *J Infect Dis* 2022; **226:** 2129–36.

14 Aggarwal NR, Beaty LE, Bennett TD, et al. Change in effectiveness of sotrovimab for preventing hospitalization and mortality for at-risk COVID-19 outpatients during an omicron BA.1 and BA.1.1-predominant phase. *Int J Infect Dis* 2022; published online October 10. https://doi.org/10.1016/j.ijid.2022.10.002.

15 Colorado Department of Public Health and Environment. COVID-19 treatments. https://covid19.colorado.gov/for-coloradans/covid-19-treatments#collapse-accordion-40911-4 (accessed Nov 1, 2022).

16 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; **46:** 399–424.

17 Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Polit Anal* 2007; **15:** 199–236.

18 Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol* 2010; **172:** 1092–97.

19 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; **10:** 150–61.

20 Nguyen T-L, Collins GS, Spence J, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol* 2017; **17:** 78.

21 National Institutes of Health. Therapeutic management of nonhospitalized adults with COVID-19. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/ (accessed Sept 9, 2022).

22 Colorado Department of Public Health and Environment. COVID-19 data. https://covid19.colorado.gov/data (accessed Oct 26, 2022).

23 Puhr R, Heinze G, Nold M, Lusa L, Geroldinger A. Firth's logistic regression with rare events: accurate effect estimates and predictions? *Stat Med* 2017; **36:** 2302–17.

24 Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med* 2002; **21:** 2409–19.

25 Heinze G, Ploner M, Dunkler D, Southworth H, Jiricka L. logistf: Firth's bias-reduced logistic regression. Oct 13, 2022. https://cran.r-project.org/web/packages/logistf/logistf.pdf (accessed Jan 12, 2023).

26 Lüdecke D, Makowski D, Ben-Shachar MS, et al. performance: an R package for assessment, comparison and testing of statistical models. *J Open Source Softw* 2021; **6:** 3139.

27 Takashita E, Yamayoshi S, Simon V, et al. Efficacy of antibodies and antiviral drugs against omicron BA.2.12.1, BA.4, and BA.5 subvariants. *N Engl J Med* 2022; **387:** 468–70.

28 Yip TCF, Lui GCY, Lai MSM, et al. Impact of the use of oral antiviral agents on the risk of hospitalization in community COVID-19 patients. *Clin Infect Dis* 2022; published online Aug 29. https://doi.org/10.1093/cid/ciac687.

29 Ganatra S, Dani SS, Ahmad J, et al. Oral nirmatrelvir and ritonavir in non-hospitalized vaccinated patients with COVID-19. *Clin Infect Dis* 2022; published online Aug 20. https://doi.org/10.1093/cid/ciac673.

30 Zhou X, Kelly SP, Liang C, et al. Real-world effectiveness of nirmatrelvir/ritonavir in preventing hospitalization among patients with COVID-19 at high risk for severe disease in the United States: a nationwide population-based cohort study. *medRxiv* 2022; published online Sept 14. https://doi.org/10.1101/2022.09.13.22279908 (preprint).

31 Shah MM, Joyce B, Plumb ID, et al. Paxlovid associated with decreased hospitalization rate among adults with COVID-19—United States, April–September 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1531–37.