Real-world use of nirmatrelvir-ritonavir in COVID-19 outpatients during BQ.1, BQ.1.1., and XBB.1.5 predominant omicron variants in three U.S. health systems: a retrospective cohort study

Neil R. Aggarwal,[a,i,*] Laurel E. Beaty,[b,i] Tellen D. Bennett,[c] Lindsey E. Fish,[d] Jason R. Jacobs,[e] David A. Mayer,[b] Kyle C. Molina,[f] Jennifer L. Peers,[f] Douglas B. Richardson,[d] Seth Russell,[c] Alejandro Varela,[b] Brandon J. Webb,[g] Matthew K. Wynia,[a,h] Mengli Xiao,[b] Nichole E. Carlson,[b] and Adit A. Ginde[f]

[a]Department of Medicine, Division of Pulmonary Sciences and Critical Care, University of Colorado School of Medicine, Aurora, CO, 80045, USA
[b]Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO, 80045, USA
[c]Departments of Biomedical Informatics and Pediatrics, University of Colorado School of Medicine, Colorado Clinical and Translational Sciences Institute, University of Colorado Anschutz Medical Campus, Aurora, 80045, USA
[d]Division of General Internal Medicine, Denver Health and Hospital and University of Colorado School of Medicine, Denver, CO, 80204, USA
[e]Pulmonology and Critical Care Medicine Research, Intermountain Health, Murray, UT, 84107, USA
[f]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, 80045, USA
[g]Division of Infectious Diseases and Clinical Epidemiology, Intermountain Health, Salt Lake City, UT, 84107, USA
[h]Department of Health Systems Management and Policy, University of Colorado Center for Bioethics and Humanities, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, 80045, USA

The Lancet Regional Health - Americas 2024;31: 100693

Published Online 9 February 2024
https://doi.org/10.1016/j.lana.2024.100693

Summary

Background Ritonavir-boosted Nirmatrelvir (NMV-r), a protease inhibitor with *in vitro* activity against SARS-CoV-2, can reduce risk of progression to severe COVID-19 among high-risk individuals infected with earlier variants, but less is known about its effectiveness against omicron variants BQ.1/BQ.1.1/XBB.1.5. We sought to evaluate effectiveness of NMV-r in BQ.1/BQ.1.1/XBB.1.5 omicron variants by comparing hospitalisation rates to NMV-r treated patients during a previous omicron phase and to contemporaneous untreated patients.

Methods We conducted a retrospective observational cohort study of non-hospitalised adult patients with SARS-CoV-2 infection using real-world data from three health systems in Colorado and Utah, and compared hospitalisation rates in NMV-r-treated patients in a BA.2/BA.2.12.1/BA.4/BA.5 variant-predominant (first) phase (April 3, 2022–November 12, 2022), with a BQ.1/BQ.1.1/XBB.1.5 variant-predominant (second) phase (November 13, 2022–March 7, 2023). In the primary analysis, we used Firth logistic regression with a two-segment (phase) linear time model, and pre-specified non-inferiority bounds for the mean change between segments. In a pre-specified secondary analysis, we inferred NMV-r effectiveness in a cohort of treated and untreated patients infected during the second phase. For both analyses, the primary outcome was 28-day all-cause hospitalisation. Subgroup analyses assessed treatment effect heterogeneity.

Findings In the primary analysis, 28-day all-cause hospitalisation rates in NMV-r treated patients in the second phase (n = 12,061) were non-inferior compared to the first phase (n = 25,075) (198 [1.6%] vs. 345 [1.4%], adjusted odds ratio (aOR): 0.76 [95% CI 0.54–1.06]), with consistent results among secondary endpoints and key subgroups. Secondary cohort analyses revealed additional evidence for NMV-r effectiveness, with reduced 28-day hospitalisation rates among treated patients compared to untreated patients during a BQ.1/BQ.1.1/XBB.1.5 predominant phase (198/12,061 [1.6%] vs. 376/10,031 [3.7%], aOR 0.34 [95% CI 0.30–0.38), findings robust to additional sensitivity analyses.

Interpretation Real-world evidence from major US healthcare systems suggests ongoing NMV-r effectiveness in preventing hospitalisation during a BQ.1/BQ.1.1/XBB.1.5-predominant phase in the U.S, supporting its continued use in similar patient populations.

*Corresponding author. Department of Medicine, University of Colorado School of Medicine, 12700 E. 19th Ave, Mail Stop C-272, Aurora, CO, 80045, USA.
E-mail address: neil.aggarwal@cuanschutz.edu (N.R. Aggarwal).
[i]Contributed equally to this manuscript.

Funding U.S. National Institutes of Health.

Keywords: Nirmatrelvir-ritonavir; COVID-19 omicron variants

Research in context

Evidence before this study

Nirmatrelvir-ritonavir (NMV-r), an oral antiviral for the treatment of high-risk outpatients with COVID-19, has been shown to lower the risk of hospitalisation, thereby improving patient outcomes and decreasing the burden of COVID-19 on the healthcare system. We searched PubMed for studies published from inception to September 1, 2023, using the search terms "Nirmatrelvir OR Paxlovid OR PF-07321332" AND "SARS-COV-2 OR COVID-19" without language restrictions. The pivotal study examining the safety and effectiveness of nirmatrelvir-ritonavir was the EPIC-HR trial, in which treatment initiation within five days of symptom onset was associated with an 88% reduced risk of COVID-19-related hospitalisation or death at 28 days. Since completion, several real-world studies across the world have demonstrated similar effectiveness of NMV-r against omicron variants including BA.4/BA.5, contributing to the knowledge necessary for full U.S. FDA and EMA approval of NMV-r for treating high-risk outpatients acutely infected with SARS-CoV-2. Furthermore, studies in Singapore and Malaysia demonstrated NMV-r effectiveness in cohorts inclusive of BQ.1/BQ.1.1/XBB.1.5 omicron variants.

Added value of this study

To our knowledge, this is one of the first U.S.-based study to examine the effectiveness of NMV-r in a cohort of non-hospitalised patients that includes a BQ.1/BQ.1.1/XBB.1.5 omicron dominant phase, and the only U.S.-based study to specifically evaluate NMV-r effectiveness during an exclusive BQ.1/BQ.1.1/XBB.1.5 omicron phase. To navigate changes in SARS-CoV-2 testing practices and high rates of test result missingness, we pre-specified a comparison between NMV-r treated patients across two omicron dominant phases. Compared to matched NMV-r treated patients during a BA.2/BA.2.12.1/BA.4/BA.5 omicron dominant phase, 28-day hospitalisation rates were similar, a finding consistent across most clinically important subgroups, indicating continued NMV-r effectiveness against newer omicron variants. These findings were supported by a secondary cohort comprised only of patients infected during the BQ.1/BQ.1.1/XBB.1.5 omicron dominant phase, in which NMV-r treated patients had much lower odds of 28-day hospitalisation as compared to untreated controls.

Implications of all the available evidence

Current international guidelines recommend nirmatrelvir-ritonavir for patients with non-severe COVID-19 at high risk of hospitalisation or death. Our study of real-world use in high-risk outpatients extends prior data by providing strong associations of nirmatrelvir-ritonavir benefit during a BQ.1/BQ.1.1/XBB.1.5 omicron dominant phase, including for patients vaccinated with three or more doses.

Introduction

Continued infectivity by SARS-CoV-2 among susceptible individuals demonstrates a need for accessible therapeutics that hasten recovery and attenuate the burden on the health care system. 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] Based on the favourable results of the EPIC-HR trial that demonstrated an 89% reduction in risk of progression in a predominantly unvaccinated outpatient SARS-CoV-2-infected population,[2] Nirmatrelvir-ritonavir (NMV-r) was granted U.S. Food and Drug Administration emergency use authorisation (EUA) for the treatment of mild-to-moderate COVID-19 in patients at high risk for progression to severe COVID-19.[3]

Current SARS-CoV-2 infections are dominated by omicron lineage variants that demonstrate high transmissibility and immune evasion, yet are generally associated with decreased disease severity compared to prior variants.[4] NMV-r has demonstrated consistent effectiveness against recent SARS-CoV-2 omicron variants, as evidenced by several observational studies.[5–11] With recent full U.S. FDA and European Medicines Agency (EMA) approval of NMV-r in high-risk outpatients, the anticipated increase in NMV-r prescriptions necessitates ongoing evaluation of its effectiveness against the omicron variants that have become dominant after BA.4/5 in the U.S.,[12] notably for BQ.1.1 and XBB.1.5 that have *in vitro* evidence of greater immune-evasion capabilities than earlier omicron variants, though remain susceptible to NMV-r.[13]

Evaluation of antiviral treatment effectiveness in a real-world setting is limited by a lack of SARS-CoV-2 home test result availability in health system EHRs, previously resulting in more than 80% test result missingness among patients prescribed antiviral therapies.[14] Coupled with a more recent trend for patients to minimise even home testing or delay treatment initiation from time of symptom,[9,15] these factors make it

challenging to accurately identify untreated patients, introducing bias in interpretation of NMV-r effectiveness in a cohort that includes untreated patients as a control population. To address this limitation, we used a real-world data platform from three health systems across Colorado and Utah to conduct a non-inferiority segmented time logistic regression analysis of a retrospective observational cohort limited only to NMV-r-treated patients, to evaluate for possible reduction in the effectiveness of NMV-r during a BQ.1/BQ.1.1/XBB.1.5 variant-predominant phase compared to an earlier omicron BA.2/BA.2.12.1/BA.4/BA.5 variant-predominant phase.

Methods

Study design and participants

We conducted an observational cohort study as a collaboration at the University of Colorado, University of Colorado Health (UCHealth), Denver Health (DH), Intermountain Health (IH), and the Colorado Department of Public Health and Environment (CDPHE).[14,16–19] The study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent. We obtained data from the electronic health record (EHR) at UCHealth, DH (Epic) and IH (Cerner) using an enterprise-wide data warehouse, and merged it with statewide data on vaccination status from the Colorado Comprehensive Immunization Information System and mortality from Colorado Vital Records. IH data included statewide vaccination and mortality records. This analysis conforms to STROBE reporting guidance (Appendix 1, p 3 and 4).

The primary variable of interest was binary omicron phase, justified by general acceptance of NMV-r effectiveness against BA.5 and prior omicron subvariants, allowing this prior phase to serve as an appropriate comparator. Therefore, the primary analysis cohort was limited to only patients treated with NMV-r in three health systems (UCHealth, DH, IH), with full details and justification stated at the pre-specified statistical analysis plan (Appendix 2). For all patients we utilised a 1-day prior imputation strategy from the NMV-r order date to the *index* date for SARS-CoV-2 positive test.[14] Patients with an index date between April 3rd, 2022 and March 7th, 2023 were included in the initial cohort (n = 99,672).

Procedures

The decision to receive antiviral treatment was made by patients and clinicians, with NMV-r as preferred therapy within 5 days of symptom onset. Based on Colorado and Utah virus strain data, we considered patients with an index date between April 3, 2022 and November 12, 2022 to be in the first phase (BA.2/BA.2.12.1/BA.4/BA.5 variant-predominant), and patients with an index date between November 13, 2022 and March 7, 2023 to be in the second phase (BQ.1/BQ.1.1/XBB.1.5 variant-predominant). Variant-predominant phases were defined by the date when publicly available sequencing data indicated that greater than 50% of patients were infected with the variants of interest (Appendix 1, Figure S1 p 5 and 6).[20,21]

The main exclusion criteria were: 1) order or administration of molnupiravir, or administration of any other SARS-CoV-2 monoclonal antibody or antiviral [including bamlanivimab, bebtelovimab, casirivimab + imdevimab, sotrovimab, tixagevimab/cilgavimab (within 10 days of SARS-CoV-2 positive date), or outpatient remdesivir] (n = 2852), 2) no orders for NMV-r (n = 57,461), and 3) index date or NMV-r treatment during hospital admission or NMV-r treatment at hospital discharge (n = 97), resulting in 39,262 NMV-r treated patients (Appendix 1, Table S1 p 11 and 12). We retained patients who were hospitalised or died later the same day as their index date, and patients who did not have an EHR-recorded EUA-qualifying condition, as not all criteria were consistently available, and subsequently varied these assumptions in pre-specified sensitivity analyses.

- To investigate the possibility of imbalanced confounders between the two variant-dominant phases in the primary cohort, we compared standardized mean differences (SMDs) between phases for all candidate variables. Because all SMDs were below the prespecified threshold of 0.1, indicating adequate balance, no balancing measures were applied to the cohort prior to the primary analysis (Appendix 1, Table S2, p 13).[22] We removed any patients missing important covariate data (n = 2120) and patients outside of the common support (n = 6). After exclusions, the final primary analysis cohort contained a total of 37,136 patients (Appendix 1, Figure S2, p 7).

For a pre-specified secondary analysis aiming to infer the effectiveness of NMV-r using an approach similar to prior studies,[14] we identified a secondary cohort that included both NMV-r treated patients and untreated patients limited only to the BQ.1/BQ.1.1/XBB.1.5 variant-predominant phase (November 13th, 2022–March 7th, 2023), n = 23,634 (Appendix 1, Figure S3, p 8, Appendix Table S3, pp 14 and 15). An untreated patient was defined as having a positive SARS-CoV-2 test in the EHR without an order for NMV-r or administration of any other COVID-19 antiviral treatment. We utilised the same imputation method for the index date as we used in the primary analysis, as well a three-day fixed difference.[14]

Variable definitions

Hospitalisation was defined as any inpatient or observation encounter documented in the EHR. We selected the first hospitalisation that occurred the same day, or

any day after the index date for NMV-r treated patients. ED visits were defined as any visit to the ED, with or without an associated inpatient or observation encounter. For NMV-r treated patients, we selected the first ED visit that occurred at least one day after the NMV-r order date, given that NMV-r treatment was often prescribed at the initial ED 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/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.

Covariates of interest included categorical age in years, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of comorbid conditions (excluding obesity, immunocompromised status), three-level COVID-19 vaccination status (0, 1–2, 3+, administered prior to the observed or imputed SARS-CoV-2 positive test), and health system defined as before and in supplement.[14,19]

EHR evidence of comorbid conditions was based on the Charlson and Elixhauser Comorbidity Indices, and along with immunocompromised status (Appendix 1, Table S4, pp.16).[14,16] Obesity and immunocompromised status were evaluated separately in the analysis from the sum of other comorbid conditions.

Outcomes

The primary outcome was all-cause hospitalisation within 28 days of the index date. COVID-19-related 28-day hospitalisation was a secondary outcome, defined as the presence of any of the following associated with the index hospitalisation: COVID-19 ICD-10 code (U07.1, J12.82, M35.81, Z20.822, M35.89), administration of inpatient remdesivir, or use of any supplemental oxygen.[14,18] The other reported secondary outcome was 28-day all-cause emergency department (ED) visits. Due to low proportions and event rates, we presented only descriptive statistics for 28-day all-cause mortality. In the hospitalised subset, exploratory outcomes included hospital length of stay (LOS), odds of ICU transfer, disease severity based on maximum level of respiratory support, and in-hospital mortality.

Statistical analysis

In the primary analysis, to evaluate differences in outcomes among NMV-r treated patients in the two variant-predominant omicron phases we fit a Firth's logistic regression to address estimation issues related to low event rates and complete separation, using the R package logistf Version 1.24.[23–25] Within this model, we created a segmented linear model for time. Specifically, we included continuous linear time and allowed both a mean shift in the model between the BQ.1/BQ.1.1/XBB.1.5 phase and prior omicron phase. We also allowed the slope on time to change in the BQ.1/BQ.1.1/XBB.1.5 phase compared to the prior omicron phase. This model for time allowed us to test the hypothesis that the impact of NMV-r on hospitalisation rates was not inferior in the BQ.1/BQ.1.1/XBB.1.5 variant-predominant phase compared to the earlier omicron variant phase, while accounting for independent changes in hospitalisation that occurred over time.

We used a pre-defined power analysis that determined non-inferiority would be declared when the upper bound of the 90% confidence interval (CI) is less than 1.33 for the intercept change to BQ.1/BQ.1.1/XBB.1.5 in the segmented linear analysis (Appendix 2). To be consistent with other clinical literature we present the 95% CI bounds. If the upper bound of the 95% CI was above 1.33 then we also present the 90% upper CI to allow for correct interpretation of the non-inferiority hypothesis. All models were adjusted for age, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of additional comorbid conditions, number of vaccinations, and health system.

We also fit a phase agnostic adjusted logistic regression with B-splines to flexibly model the relationship between continuous days in the study and the odds of hospitalisation. We tested a variety of different numbers and locations based on percentiles of knots and selected the best model based on a likelihood ratio test (LRT) and parsimony. We then used this model to visualize the flexible association between time and hospitalisation and identify any large misspecification using the time model described above (none were identified).

We estimated adjusted omicron phase effects for seven subgroups of interest by fitting interaction models that were also adjusted for all variables of interest. Each model included an interaction between the subgroup of interest and the binary phase term, which allowed us to estimate several mean changes by subgroup. The subgroups of interest included binary age (<65 vs. ≥65), binary obesity status, binary (yes vs. no) and three-level immunocompromised status (no, mild, and moderate/severe), binary number of comorbidities (0–1 vs. ≥2), binary (0 vs. ≥1) and three-level vaccination status (0, 1–2, and ≥3), three-level race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Black/other), and binary sex (male, female).

We performed two pre-specified sensitivity analyses in the primary analysis cohort. One analysis included only patients with an observed SARS-CoV-2 positive test that was used as the index date, and a second analysis removed all patients who had their order for NMV-r prescription on the same date as their first hospitalisation. For both sensitivity analyses we refit the primary 28-day all-cause hospitalisation adjusted logistic regression model and conducted the non-inferiority hypothesis testing. Post-hoc sensitivity analyses included (1) excluding patients with renal disease, (2) replacing

adjustment for number of vaccine doses with adjustment for duration since last vaccine dose (unvaccinated, 0–3, 3–6, 6–9, and >9 months) (vaccine reparameterization), and (3) utilizing a stricter cut-off (80% presence of dominant variants) to define cohort phases.

In pre-specified secondary analysis, we refit the primary adjusted Firth's logistic regression model to a cohort of NMV-r treated and untreated patients uniquely from the second BQ.1/BQ.1.1/XBB.1.5 phase (Appendix 1, Table S3, p 14 and 15), and applied inverse probability weighting (IPW) for treatment status after removing patients with missing covariate data. Excluding patients with an IPW outside of 0.1 and 0.9, the final sample size n = 22,092 (Appendix 1, Table S5, p 17 and 18). We then conducted complementary pre-specified sensitivity analyses on the secondary model: First, we limited the cohort to only patients with EHR-derived data on EUA-qualifying conditions (Appendix 1, Table S6, p 18) (n = 20,398) (Appendix 1, Table S7, p 19 and 20). Second, we selected only patients with an observed SARS-CoV-2 positive test and used this as the index date, subsequently removing patients with an index date not in 11/13/22–3/7/23, and patients who had their SARS-CoV-2 positive test while in the hospital (n = 13,182) (Appendix 1, Table S8, p 21 and 22). For the third sensitivity analysis, we removed patients with either an observed SARS-CoV-2+ test or an NMV-r order date on the same date as their first hospitalisation (n = 21,891) (Appendix 1, Table S9, p 23 and 24). A post-hoc secondary analysis utilized IPW with a three-day index imputation method for the treated population (n = 21,972) (Appendix 1, Table S10, pp 25–26).

All statistical analyses were performed using R Statistical Software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The study funder had no role in study design, data collection, analysis or interpretation, writing of the report, or decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Among 99,672 patients with a positive SARS-CoV-2 test or treatment in the overall study period, 37,136 NMV-r patients met study inclusion criteria, of which 12,061 patients had an index date during the latter Omicron phase dominated by BQ.1/BQ.1.1/XBB.1.5 variants. 71 percent of patients (26,353/37,136) in the primary cohort of NMV-r treated patients did not have an observed SARS-CoV-2 test date. All patients had at least 28 days of follow-up. Baseline patient characteristics between the two omicron phases were similar (Table 1), and with all variables of interest having an SMD below 0.1 (Appendix 1, Table S2, p 13).

Characteristic	BA.2/BA2.12.1/BA.4/BA.5 (n = 25,075)	BQ.1/BQ.1.1/XBB.1.5 (n = 12,061)
Age group[b]		
18–44 years	5832 (23.3%)	2655 (22.0%)
45–64 years	8451 (33.7%)	4063 (33.7%)
≥65 years	10,792 (43.0%)	5343 (44.3%)
Female sex	14,593 (58.2%)	7092 (58.8%)
Race/Ethnicity		
Non-Hispanic white	20,675 (82.5%)	9732 (80.7%)
Hispanic	2619 (10.4%)	1461 (12.1%)
Non-Hispanic black	609 (2.4%)	294 (2.4%)
Other	1172 (4.7%)	574 (4.8%)
Insurance status[a,b]		
Private/Commercial	12,457 (49.7%)	5622 (46.6%)
Medicare	10,157 (40.5%)	5072 (42.1%)
Medicaid	1635 (6.5%)	949 (7.9%)
None/Uninsured	433 (1.7%)	240 (2.0%)
Other/Unknown	393 (1.6%)	178 (1.5%)
Immunocompromised[b]		
Mild	3250 (13.0%)	1754 (14.5%)
Moderate/Severe	3462 (13.8%)	1596 (13.2%)
Obese[b]	7944 (31.7%)	3893 (32.3%)
Number of other comorbid conditions		
One	7326 (29.2%)	3526 (29.2%)
Two or more	10,315 (41.1%)	5213 (43.2%)
Diabetes mellitus	4905 (19.6%)	2400 (19.9%)
Cardiovascular disease	5238 (20.9%)	2514 (20.8%)
Pulmonary disease	9087 (36.2%)	4655 (38.6%)
Renal disease	2260 (9.0%)	1021 (8.5%)
Hypertension	11,733 (46.8%)	5875 (48.7%)
Liver disease		
Mild	3224 (12.9%)	1693 (14.0%)
Severe	155 (0.6%)	93 (0.8%)
Number of vaccinations prior to SARS-CoV-2+ date[b]		
0	4484 (17.9%)	2173 (18.0%)
1	1010 (4.0%)	440 (3.6%)
2	3744 (14.9%)	1683 (14.0%)
3+	15,837 (63.2%)	7765 (64.4%)

Abbreviations: NMV-r, Nirmatrelvir-ritonavir. [a]Private/commercial insurance and Medicare collapsed for multivariable models due to collinearity between age and Medicare insurance. [b]Checked for imbalance between the two Omicron phases.

Table 1: **Baseline characteristics by omicron phase for primary analytic cohort.**

Among NMV-r treated patients, odds of hospitalisation during the omicron BQ.1/BQ.1.1/XBB.1.5 variant-predominant second phase were not increased (non-inferior) compared to the BA.2/BA.2.12.1/BA.4/BA.5 variant-predominant first phase, adjusted odds ratio (aOR) 0.76, with 95% upper confidence limit for intercept change within the pre-specified range (0.54–1.06). Over the entire study period, raw 28-day all-cause hospitalisation rates (1.6% second phase vs. 1.4% first phase (Table 2)) and odds of hospitalisation in the segmented linear analysis (aOR = 1.00, p = 0.0019) increased, but predominantly within first phase and not during the comparator BQ.1/BQ.1.1/XBB.1.5 s phase

Outcome	BA.2/BA2.12.1/BA.4/BA.5	BQ.1/BQ.1.1/XBB.1.5	Adjusted OR (95% CI)
Overall sample size	**n = 25,075**	**n = 12,061**	
All-cause 28-day hospitalisation	345 (1.4%)	198 (1.6%)	0.76 (0.54–1.06[b])
COVID-related 28-day Hospitalisation[a]	273 (1.1%)	164 (1.4%)	0.71 (0.49–1.03[b])
All-cause 28-day ED visit	1103 (4.4%)	556 (4.6%)	1.00 (0.82–1.23[b])
All-cause 28-day mortality	17 (0.1%)	14 (0.1%)	–
Hospitalised sample size	**n = 345**	**n = 198**	
Hospital LOS, days, mean (SD)	3.7 (4.1)	3.8 (3.8)	–
ICU level of care	44 (12.8%)	28 (13.1%)	–
Max level of resp. support			–
No oxygen	124 (35.9%)	57 (28.8%)	
Standard oxygen	186 (53.9%)	117 (59.1%)	–
HHFNC/NIV	25 (7.2%)	17 (8.6%)	–
IMV	5 (1.4%)	3 (1.5%)	–
Death	5 (1.4%)	4 (2.0%)	–
Sensitivity analyses			
Observed SARS-CoV-2+ test (n = 10,716)	220/7545 (2.9%)	122/3171 (3.8%)	0.77 (0.51–1.17[b])
Exclude same-day hospitalisations (n = 37,059)	297/25,027 (1.2%)	169/12,032 (1.4%)	0.77 (0.53–1.10[b])
Exclude patients with renal disease (n = 33,855)	261/22,815 (1.1%)	154/11,040 (1.4%)	0.79 (0.54–1.16[b])
Vaccine reparameterization (n = 37,136)	345 (1.4%)	198 (1.6%)	0.80 (0.57–1.11[b])
80% dominant variant cohort phases (n = 29,126)	299/22,250 (1.3%)	113/6876 (1.6%)	0.77 (0.51–1.16[b])

All regression models adjusted for age, sex, race/ethnicity, obesity, immunocompromised status, number of comorbidities, insurance status, vaccination status, and health system. Abbreviations: NMV-r, Nirmatrelvir-ritonavir; OR, odds ratio; CI, Confidence Interval; LOS, Length of Stay; ICU, Intensive Care Unit. [a]COVID-related hospitalisation was defined by presence of COVID-19 ICD-10 codes (U07.1, J12.82, M35.81, Z20.822, M35.89), administration of inpatient remdesivir, or use of supplemental oxygen. [b]Compared to an *a priori* upper CI threshold of 1.33.

Table 2: **Primary and secondary outcomes for NMV-r treatment for primary cohort and sensitivity analyses.**

(aOR = 1.00, p = 0.49) (Appendix 1, Table S11, p 27). An adjusted spline curve plot further illustrates the slope change during the first phase, followed by a plateau in the log-odds of 28-day hospitalisation that persists through the BQ.1/BQ.1.1/XBB.1.5 phase (Fig. 1). Collectively, these data suggest that the odds of 28-day hospitalisation in NMV-r-treated patients were similar (within the pre-specified non-inferiority parameters) in patients treated during the BQ.1/BQ.1.1/XBB.1.5 variant-predominant phase compared to those in the earlier BA.2/BA.2.12.1/BA.4/BA.5 phase.

Within the primary cohort, 80.5% (437/543) of all hospitalisations were deemed to be COVID-related based on defined criteria,[14,18] and the time effect variable for COVID-related hospitalisations was similar to the primary model (BQ.1/BQ.1.1/XBB.1.5 95% UCL 1.03, aOR 0.71) (Table 2). We observed a similar trend for 28-day ED after NMV-r treatment (BQ.1/BQ.1.1/XBB.1.5 95% UCL 1.23, aOR 1.00). Mortality rates and higher levels of respiratory support (IMV, HHFNC) were very low and nominally similar in both phases. ICU admission rates (13.1% vs. 12.8%) and mean hospital length of stay (3.8 vs. 3.7 days) among hospitalised patients were also similar between in the BQ.1/BQ.1.1/XBB.1.5 phase vs prior omicron phase, and all in-hospital outcomes were reported using descriptive statistics only due to very low event rates (Table 2).

The phase effect was consistent across defined subgroups of interest, and no interaction p-values were statistically significant (Appendix 1, Figure S5, p 10, Appendix Table S12, p 28 and 29). Notably, estimates among a three-level race/ethnicity subgroup were similar to the overall primary cohort aOR (non-Hispanic white aOR 0.75 (265/20,675, 1.28% vs. 143/9732, 1.47%), Hispanic aOR 0.84 (51/2619, 1.95% vs. 39/1461, 2.67%), Non-Hispanic Black/other aOR 0.73 (29/1781, 1.63% vs. 16/868, 1.84%)), as were the estimates in a two-level sex subgroup (Female aOR 0.77 (209/14,593, 1.43% vs. 122/7092 (1.72%), Male aOR 0.75 (136/10,482, 1.30% vs. 76/4969, 1.53%)). Both pre-specified sensitivity analyses, evaluating only NMV-r treated patients with observed SARS-CoV-2 positive tests or excluding patients with hospitalisation the same day as their index date, revealed ORs consistent with the primary analysis (Table 2), with full demographic results provided in the Appendix (Appendix 1, Tables S13 and S14, p 30 and 31). Three post-hoc sensitivity analyses, excluding patients with renal disease, vaccine reparameterization based on time since last dose, or tightening cohort phase criteria to 80% dominant variant presence revealed ORs consistent with the primary analysis (Table 2) with full demographic results provided (Appendix 1, Tables S15–S17), pp 32–34). Patients excluded due to missing covariate data (2126/39,262 5.4% of the primary cohort) were similar in distribution

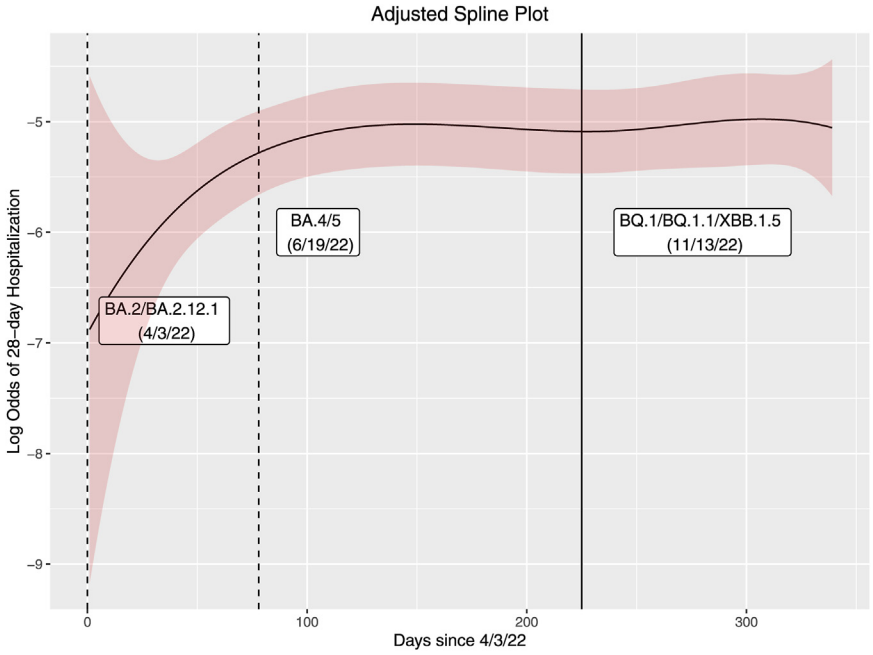

***Fig. 1:* Adjusted spline plot for time and log odds of 28-day all-cause hospitalisation.** This figure is a result of the adjusted model that includes a natural b-spline with 2 knots. The solid line represents the transition to infection by BQ.1/BQ.1.1/XBB.1.5 of at least 51% of patients that served as the comparator group in the primary cohort. Each dashed line indicates when respective prior omicron phases had infected at least 51% of patients.

of demographic factors or co-morbid conditions, with missingness mostly commonly due to race/ethnicity, obesity, or number of other comorbid conditions variable being unavailable; 28-day all-cause hospitalization rates were similar when evaluating the primary analytic cohort compared to the excluded cohort by omicron phase (Appendix 1, Table S18), p 35.

All adjusted treatment estimates for the secondary cohort during a BQ.1/BQ.1.1/XBB.1.5 predominant phase provided evidence that there is a significant reduction in the odds of 28-day hospitalisation for NMV-r treated patients in comparison to untreated patients (Appendix 1, Table S19, p 36). In the IPW analysis, the aOR was 0.34 ($p < 0.0001$) with a NNT = 47 while including the inverse treatment propensity weights in the model. This result was consistent in the EUA-eligible only analysis (treatment aOR = 0.33, $p < 0.0001$, NNT = 38), the observed SARS-CoV-2 test result only analysis (aOR = 0.70, $p = 0.0010$, NNT = 475), excluding patients hospitalised on the same day as a positive SARS-CoV-2 test or NMV-r order date (aOR = 0.51, $p < 0.0001$, NNT = 150), and using IPW with a three-day imputation method (aOR = 0.33, $p < 0.0001$, NNT = 46) (Appendix 1, Table S19, pp 36).

Discussion

In a primary cohort of 37,136 NMV-r treated patients in three health systems across Colorado and Utah, we observed similar odds of 28-day all-cause hospitalisation and 28-day COVID-related hospitalisation during a BQ.1/BQ.1.1/XBB.1.5 predominant omicron phase as compared to a BA.2/BA.2.12.1/BA.4/BA.5 predominant omicron phase. These findings of continued NMV-r effectiveness against newer omicron variants are supported by a secondary cohort only of patients infected during a BQ.1/BQ.1.1/XBB.1.5 predominant phase that revealed an IPW-calculated aOR of 0.34 for 28-day all-cause hospitalisation among NMV-r treated patients as compared to untreated patients. Supported by pre-specified sensitivity analyses that help address limitations in our study design, we believe these results are among the first to suggest the effectiveness of NMV-r among high-risk outpatients during a BQ.1/BQ.1.1/XBB.1.5 predominant phase in the United States,[11] and are comparable to results derived from Singapore and Malaysia cohorts inclusive of XBB-infected participants.[26,27]

With real-world, contemporaneous data derived from three health systems, including the largest in Colorado and Utah, our findings that support continued effectiveness of NMV-r among high-risk outpatients infected with recent omicron variants are particularly important in anticipation of increased NMV-r use following full FDA authorisation and a seasonal uptick of infection rates in the U.S, even though current hospitalisation rates are low. Further, our results support evidence of effective NMV-r neutralization of omicron variants

in vitro, including against the XBB.1.5 variant that can effectively evade immunity induced by mRNA vaccines or natural infection but is still neutralised by a bivalent vaccine (ancestral and BA.4/5).[28,29]

In our primary cohort, results were consistent across subgroups of interest including age, comorbidities, immunocompromised state, and vaccination status (except perhaps the subgroup with one-two prior vaccine doses). Notably, nearly two-thirds of patients in the primary cohort had received three or more vaccine doses, yet NMV-r appears to retain effectiveness in this group even with exposure to newer omicron variants. Yet, with evidence that vaccine effectiveness against SARS-CoV-2 infection and symptomatic disease significantly wanes within six months,[30] continued evaluation of antiviral treatments against newer variants seems critical as newer bivalent vaccines are in production.

Limitations

This study has a few noteworthy limitations. As in any observational study, we cannot exclude residual and unmeasured confounding. We attempted to minimise confounding biases by adjusting for demographic and clinical factors that might be associated with exposure and outcomes of interest, and executed sensitivity analyses of treatment eligible study populations. Although approximating U.S. state levels, the overall proportion of non-Hispanic Blacks in our cohort is notably lower than the proportion in the U.S. population, suggesting our results are less generalizable to this important racial subgroup. Symptom duration was not reliably available in our EHR dataset so we are unable to confirm symptom onset within 5 days among patients treated with NMV-r, or recrudescence of symptoms after treatment. Given the use of EHRs to report patient-level data, it is also possible that treatment, as well as most outcomes, may have occurred elsewhere leading to misclassification – less of a concern for mortality since we have statewide data available. Although we anticipate a similar propensity for hospitalisation within the health system between untreated and NMV-r treated patients, if untreated patients were more likely to be hospitalised outside this health system, or if patients prescribed NMV-r did not fill the medication or took less than all 5 days of prescribed treatment, our results may be biased toward the null. This limitation is somewhat mitigated too by the primary analysis that included only NMV-r treated patients and the added assumption that these behaviours would not change by variant given the stable administration of NMV-r during this time period.

SARS-CoV-2 test result missingness was high and unbalanced in prior cohorts, thus limiting our ability to directly compare treated vs. untreated controls in the primary analysis. We also do not have access to patient-level sequencing, nor we are not able to accurately track recurrent SARS-CoV-2 infection rates, and thus are unable to evaluate the importance of these variables in our analyses. With a shift in practice to even more limited home testing, we elected to compare two different NMV-r treated groups in our primary cohort. The pre-specified sensitivity analysis using only patients with an observed SARS-CoV-2+ test date revealed a similar point estimate for NMV-r association with reduced 28-day hospitalisation between omicron phases. As before, we also did not exclude hospitalisations on the date of NMV-r order in the primary cohort analysis.[14] Recognising this approach may introduce bias, we were reassured that a pre-specified sensitivity analysis excluding patients hospitalised the same day as their NMV-r order revealed statistically similar results.

Conclusion

Prior observational studies have consistently demonstrated the effectiveness of NMV-r to reduce hospitalisation among high-risk adults. Across three health systems in Colorado and Utah, our results of similar odds of hospitalisation among NMV-r treated patients during a BQ.1/BQ.1.1/XBB.1.5 predominant phase as compared to a BA.2/BA.2.12.1/BA.4/BA.5 predominant phase, as well as reduced odds of hospitalisation compared to untreated controls in a secondary cohort of patients predominantly infected with the BQ.1/BQ.1.1/XBB.1.5, suggest continued effectiveness of NMV-r against the most recent omicron variants.

Contributors

AAG conceived and obtained funding for the study. NRA, LEB, NEC, and AAG designed the study. LEB and NEC analysed the data. LEB, TDB, NEC, DAM, SR, AV, LEF, DBR, JRJ, BJW, and MX accessed and verified the raw data. NRA and LEB drafted the original version of the manuscript, and AAG, NEC, MKW, JLP, KM, BJW, LEF, and TDB provided contructive feedback leading to revised versions. All authors had full access to the data, reviewed the manuscript, contributed to data interpretation, approved the final version and accepted responsibility following a decision to submit for publication by NRA, LEB, NEC, and AAG.

Data sharing statement

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 with a signed data access agreement and approval by the project steering committee via communication with the corresponding author (neil.aggarwal@cuanschutz.edu), for researchers to reproduce results.

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. BJW reports institutional grant support for serving as a investigator for

COVID clinical trials sponsored by US Administration for Strategic Preparedness and Response (ASPR) Biomedical Advanced Research and Development Authority (BARDA), NHLBI, Gilead, Regeneron, Abbvie, Roche/Genetech for which he received no direct remuneration, All other authors declare no competing interests.

Acknowledgements

Funded by National Center for Advancing Translational Sciences of the National Institutes of Health. Supported by the Health Data Compass Data Warehouse project (healthdatacompass.org).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100693.

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