Effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system

Joseph A Lewnard, John M McLaughlin, Debbie Malden, Vennis Hong, Laura Puzniak, Bradley K Ackerson, Bruno J Lewin, Jeniffer S Kim, Sally F Shaw, Harpreet Takhar, Luis Jodar, Sara Y Tartof

Summary

Background In the USA, oral nirmatrelvir–ritonavir is authorised for use in patients aged 12 years or older with mild-to-moderate COVID-19 who are at risk of progression to severe disease and hospitalisation. We aimed to establish the effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and death in people with COVID-19 in an outpatient prescribing context in the USA.

Methods In this matched observational outpatient cohort study in the Kaiser Permanente Southern California (CA, USA) health-care system, data were extracted from electronic health records of non-hospitalised patients aged 12 years or older who received a positive SARS-CoV-2 PCR test result (their index test) between April 8 and Oct 7, 2022, and had not received another positive test result within the preceding 90 days. We compared outcomes between people who received nirmatrelvir–ritonavir and those who did not receive nirmatrelvir–ritonavir by matching cases by date, age, sex, clinical status (including care received, the presence or absence of acute COVID-19 symptoms at testing, and time from symptom onset to testing), vaccination history, comorbidities, health-care seeking during the previous year, and BMI. Our primary endpoint was the estimated effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions or death within 30 days of a positive test for SARS-CoV-2.

Findings 7274 nirmatrelvir–ritonavir recipients and 126 152 non-recipients with positive SARS-CoV-2 tests were included in our study. 5472 (75·2%) treatment recipients and 84 657 (67·1%) non-recipients were tested within 5 days of symptom onset. Nirmatrelvir–ritonavir had an overall estimated effectiveness of 53·6% (95% CI 6·6–77·0) in preventing hospital admission or death within 30 days of a positive test for SARS-CoV-2, which increased to 79·6% (33·9–93·8) when nirmatrelvir–ritonavir was dispensed within 5 days of symptom onset. Within the subgroup of patients tested within 5 days of symptom onset and whose treatment was dispensed on the day of their test, the estimated effectiveness of nirmatrelvir–ritonavir was 89·6% (50·2–97·8).

Interpretation In a setting with high levels of COVID-19 vaccine uptake, nirmatrelvir–ritonavir effectively reduced the risk of hospital admission or death within 30 days of a positive outpatient SARS-CoV-2 test.

Funding US Centers for Disease Control and Prevention and US National Institutes of Health.

Lancet Infect Dis 2023

Published Online March 15, 2023 https://doi.org/10.1016/S1473-3099(23)00118-4

See Online/Comment https://doi.org/10.1016/S1473-3099(23)00180-9

Division of Epidemiology and Division of Infectious Diseases and Vaccinology, School of Public Health, and Center for Computational Biology, College of Engineering, University of California, Berkeley, Berkeley, CA, USA (J A Lewnard PhD); **Pfizer, New York, NY, USA** (J M McLaughlin PhD, L Puzniak PhD, L Jodar PhD); **Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA** (D Malden DPhil, V Hong MPH, B K Ackerson MD, B J Lewin MD, J S Kim PhD, S F Shaw DrPH, H Takhar MPH, S Y Tartof PhD); **Department of Health Systems Science, Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, CA, USA** (S Y Tartof)

Correspondence to: Dr Joseph A Lewnard, University of California, Berkeley, Berkeley, CA 94720, USA **jlewnard@berkeley.edu**

Introduction

Therapeutic drugs to prevent severe outcomes from SARS-CoV-2 infection are central to efforts to mitigate the burden of COVID-19 (in conjunction with vaccination as primary prevention). In early trials, neutralising monoclonal antibody therapies and remdesivir efficaciously prevented hospital admissions compared with placebo when administered early in the disease course.[1] However, the need to administer these treatments by intravenous infusion has restricted their broad implementation in ambulatory-care settings. Additionally, many monoclonal antibody therapies have been rendered ineffective by mutations in the spike protein of SARS-CoV-2.[2] In the randomised phase 2 and 3 EPIC-HR trial,[3] which was done in unvaccinated adults at high risk of serious illness who tested positive for SARS-CoV-2 in outpatient settings,[3] oral nirmatrelvir–ritonavir reduced the risk of subsequent COVID-19-related hospital admissions by 89% compared with placebo in the 28 days after treatment was dispensed. On the basis of these findings, the US Food and Drug Administration issued emergency use authorisation for nirmatrelvir–ritonavir in adults and children aged 12 years or older who are diagnosed with mild-to-moderate COVID-19, weigh at least 40 kg, and are at high risk of progression to severe disease.

After the broad introduction of nirmatrelvir–ritonavir as a treatment for COVID-19 in ambulatory-care settings, evidence is needed on its effectiveness in preventing severe disease in real-world settings. In observational studies,[4–10] nirmatrelvir–ritonavir was estimated to confer 21–79% reductions in the risk of hospital admission or other severe endpoints compared with usual care. The

Research in context

Evidence before this study

We searched PubMed with the terms ((“nirmatrelvir”) OR (“nirmatrelvir-ritonavir”) AND (COVID-19 OR SARS-CoV-2) AND (“outcome*”)) NOT ((review) OR (editorial) OR (“case report”)) for articles published in English up to Dec 4, 2022. We identified eight articles via our search, and nine additional relevant articles via forward and reverse citation tracking from the articles identified by our search. In the randomised controlled EPIC-HR trial, early treatment with oral nirmatrelvir–ritonavir was associated with an 89% reduction in hospitalisation or death compared with usual care among unvaccinated outpatients with mild-to-moderate COVID-19 at risk of severe illness. The most relevant, large, real-world effectiveness studies in highly vaccinated populations included a study based on data from an integrated health-care system in Israel, in which, compared with usual care, treatment with nirmatrelvir–ritonavir was associated with a 63% reduction in COVID-19-related hospitalisations among 2484 people aged 65 years or older at high risk of serious illness. In another study done in Israel, in which 4737 people with COVID-19 at high risk of serious illness were given nirmatrelvir–ritonavir, treatment was associated with an estimated 46% reduction in related severe illness or mortality over 28 days compared with no treatment. Similarly, data from a large US health-care system in Massachusetts during the omicron wave suggested an approximate 45% reduction in the risk of COVID-19-related hospitalisation within 14 days of diagnosis among 6036 cases aged 50 years or older treated with nirmatrelvir–ritonavir compared with untreated controls. Findings from a large study of US electronic health records suggested that nirmatrelvir–ritonavir was associated with a 51% reduction in hospital admissions compared with no treatment among people aged 18 years or older. Finally, a study in Hong Kong of the 30-day risk of COVID-19-related hospital admission showed a 24% reduction in risk with nirmatrelvir–ritonavir use compared with no treatment in the community setting. However, most of these studies were done during the first months after nirmatrelvir–ritonavir was licensed, when treatment access might have been restricted to people perceived to be at the greatest risk of severe outcomes from COVID-19. Furthermore, because these observational studies of nirmatrelvir–ritonavir did not include data for time since symptom onset for most or all cases, ability to account for potential differences in the clinical status of people receiving or not receiving nirmatrelvir–ritonavir was highly restricted. Although in some studies date of clinical SARS-CoV-2 testing was used as a proxy for symptom onset, this approach is limited by the fact that many people might wait to seek clinical testing. Data for the effectiveness of nirmatrelvir–ritonavir 0–5 days after symptom onset in preventing hospitalisation and other adverse clinical outcomes of infection with the omicron variant of SARS-CoV-2 in highly vaccinated populations remain scarce.

Added value of this study

In this matched cohort study of data from a large, integrated US health-care system, receipt of nirmatrelvir–ritonavir within 5 days of symptom onset was 80% effective in reducing the risk of hospital admission or death within 30 days of an outpatient positive SARS-CoV-2 test. Irrespective of time of dispensing, nirmatrelvir–ritonavir was 54% effective in reducing the risk of hospital admission or death within 30 days. To our knowledge, our study is one of the first large real-world effectiveness studies done during the BA.2 and BA.4 and BA.5 omicron waves in a broad representative patient population of mostly vaccinated adults that includes people younger than 65 years. Furthermore, our study had access to data about clinical status at the time of testing and treatment (including dates of symptom onset), which enabled assessment of the effectiveness of nirmatrelvir–ritonavir against severe outcomes by timing of treatment initiation.

Implications of all the available evidence

In conjunction with vaccination as a primary prevention strategy, nirmatrelvir–ritonavir can help to prevent hospital admission or death when used to treat COVID-19 in an outpatient setting in the context of high seroprevalence and wide uptake of COVID-19 vaccines. Early treatment (ie, ≤5 days after symptom onset) was associated with the greatest clinical benefit.

factors explaining the wide range of estimates remain uncertain. Although the timing of treatment initiation might be of crucial importance, previous studies have not included data about the time since onset of symptoms, making comparisons of results across studies difficult. Additionally, expansions in access to, and availability of, nirmatrelvir–ritonavir have led to widening uptake among a broad population, including younger people, people vaccinated against SARS-CoV-2 infection, and people without high-risk chronic comorbid conditions, all of which could contribute to potential variation in efficacy estimates across studies.[11,12] Furthermore, roll-out of nirmatrelvir–ritonavir has occurred during a time dominated by circulation of BA.2, BA.4, and BA.5 omicron lineages when most people in the USA and other countries have antibody evidence of previous SARS-CoV-2 infection.[13] By contrast, in the EPIC-HR trial, participants were assigned to either nirmatrelvir–ritonavir or placebo within the first 5 days of symptom onset, only unvaccinated adults at high risk (eg, older, chronically ill, with obesity) without a history of previous infection were enrolled, and the delta (B.1.617.2) variant, which has been associated with increased disease severity,[14] was the dominant circulating variant.

Although US data have shown that COVID-19-related presentation to emergency departments and hospital admissions are infrequent among people receiving nirmatrelvir–ritonavir in ambulatory-care settings,[15] systematic assessments of treatment effectiveness have

not been done. We therefore aimed to estimate the effectiveness of nirmatrelvir–ritonavir in preventing severe outcomes of SARS-CoV-2 infection in an outpatient setting in a large, integrated US health-care system.

Methods

Study setting and participants

We did a retrospective cohort study within Kaiser Permanente Southern California (KPSC), a comprehensive health-care system that provides integrated care across virtual, outpatient, emergency department, and inpatient settings to 4·7 million people (approximately 19% of the population of southern California, USA). People are enrolled in the system through employer-provided, prepaid, and federally sponsored insurance plans. The socioeconomic and ethnic and racial demographics of people within the KPSC network are broadly similar to those of the geographical areas served. Electronic health records capture all within-network care delivery, including diagnoses, medications dispensed, laboratory tests and results, and vaccinations received. Care received outside the network is captured through insurance claim reimbursements. COVID-19 vaccinations received outside KPSC were captured through linkage with the California Immunization Registry (to which providers were required to report all COVID-19 vaccine administrations within 24 h[16]), and with other health systems using the same electronic health record system.

Eligible participants were aged at least 12 years at the time of the index test, received a positive SARS-CoV-2 PCR test result (their index test) between April 8 and Oct 7, 2022 (a time when ≥5% of outpatient-diagnosed people with COVID-19 were receiving nirmatrelvir–ritonavir), had not had another positive test result within the preceding 90 days, were not hospitalised at the time of their index test or within the preceding 7 days; and were continuously enrolled in KPSC health plans for at least 1 year before their index test (allowing for a 45-day gap to account for potential delays in membership renewal). Ethical approval for the study was provided by the KPSC institutional review board, which also waived the need for informed consent.

Procedures

The primary exposures were outpatient receipt of nirmatrelvir–ritonavir (300 mg nirmatrelvir and 100 mg ritonavir taken orally twice daily for 5 days) within 5 days of symptom onset, and outpatient receipt of nirmatrelvir–ritonavir at any time after testing positive for SARS-CoV-2 (irrespective of the presence or timing of symptoms). We considered participants to be exposed to nirmatrelvir–ritonavir from the date of dispensing, as recorded in KPSC pharmacy records or adjudicated out-of-network insurance claims. People who received nirmatrelvir–ritonavir 1 day or more after their index test were considered unexposed during the time between their index test and the dispensing date. Other antiviral or monoclonal antibody treatments for COVID-19 were used sparingly (appendix p 3); additional details about nirmatrelvir–ritonavir prescribing in patients taking concomitant medications are in the appendix (p 2).

See Online for appendix

Data for acute symptoms associated with COVID-19 were extracted from structured questionnaires given with each SARS-CoV-2 test order, and from unstructured text fields within electronic health records as described previously.[17] Timing of symptom onset was defined as the earliest date on which people reported acute fever, cough, headache, fatigue, dyspnoea, chills, sore throat, myalgia, anosmia, diarrhoea, vomiting or nausea, or abdominal pain within 14 days before or after their index test date. Additional variables recorded at the time of index test included age, sex, race and ethnicity, BMI, current or former smoking status, socioeconomic status (measured by census-tract neighbourhood deprivation index[18] quintiles), number of COVID-19 vaccine doses received, previous documented SARS-CoV-2 infection, comorbidities (from which we computed Charlson comorbidity index values[19]), health-care use in the previous year (including encounters across outpatient, emergency department, and inpatient settings), and receipt of other vaccines.

Endpoints

The primary endpoint of this study was hospital admission or death from any cause within 30 days of the index positive SARS-CoV-2 test. This endpoint was selected for its similarity to the endpoint in the EPIC-HR trial,[3] in which COVID-19-related hospital admission or death from any cause after a positive test was measured. Hospital admission was considered to represent an internally consistent disease-severity threshold within our sample because standardised clinical criteria[20] were used to refer people at high risk of serious illness for assessment in emergency departments and for inpatient admission (appendix p 2). We also assessed admission to intensive care units (ICUs), requirement of mechanical ventilation, or death within 60 days of the index test date as a secondary endpoint (suggesting progression to severe disease).

Statistical analysis

We assessed changes in clinical outcomes associated with nirmatrelvir–ritonavir in a matched cohort framework, in which we monitored participants from their index test to the occurrence of each study endpoint or censoring (at the scheduled end of follow-up, study end, or disenrolment from the KPSC health system). We updated participants' treatment assignments on the date of treatment dispensing. We calculated adjusted hazard ratios and associated 95% CIs for comparisons of outcomes among people who received nirmatrelvir–ritonavir and those who did not receive nirmatrelvir–ritonavir via Cox proportional hazards models. We defined cluster-robust SEs to account

for multiple observations from people whose treatment status changed during follow-up. We verified the proportional hazards assumption by testing for non-zero slopes of Schoenfeld residuals.[21] Additional details on the regression framework are presented in the appendix (p 2). For each endpoint, we then used these adjusted hazard ratios to calculate the treatment effectiveness of nirmatrelvir–ritonavir as: Treatment effectiveness = (1 − adjusted hazard ratio) × 100%. To mitigate confounding driven by factors associated with the likelihood of both receiving nirmatrelvir–ritonavir and experiencing severe clinical outcomes, we constructed a directed acyclic graph identifying a minimal set of covariates for statistical adjustment (appendix p 24). We defined regression strata (matches) among people with COVID-19 on the basis of their week of SARS-CoV-2 testing, age, sex, timing of symptom onset in relation to testing, health-care use during the previous year, number of COVID-19 vaccine doses received, presence of comorbidities, and BMI (appendix p 2). We measured clinical status according to two criteria: receipt of care at an appointment on or within 1 day before a positive SARS-CoV-2 test (across emergency department, urgent care, outpatient, and virtual appointment settings, excluding other informal telephone encounters), and days from symptom onset, or absence of acute symptoms, at the start of the observation period. Because prescribing guidelines assign differing priority to people with one or more risk factors (eg, age, obesity, comorbidity, being unvaccinated or undervaccinated),[1] and interactions are present in the effects of these risk factors on the likelihood of developing severe disease,[22,23] this approach was selected to allow for differing baseline hazards across all combinations of the listed covariates. Other variables were included as model covariates for adjustment (appendix p 2). We populated missing data for smoking status, BMI, and neighbourhood deprivation index via multiple imputation, pooling parameter estimates across analyses with five completed pseudo-datasets.[24]

We repeated analyses in subgroups who received at least two or at least three COVID-19 vaccine doses, and among individuals who met criteria for receipt of

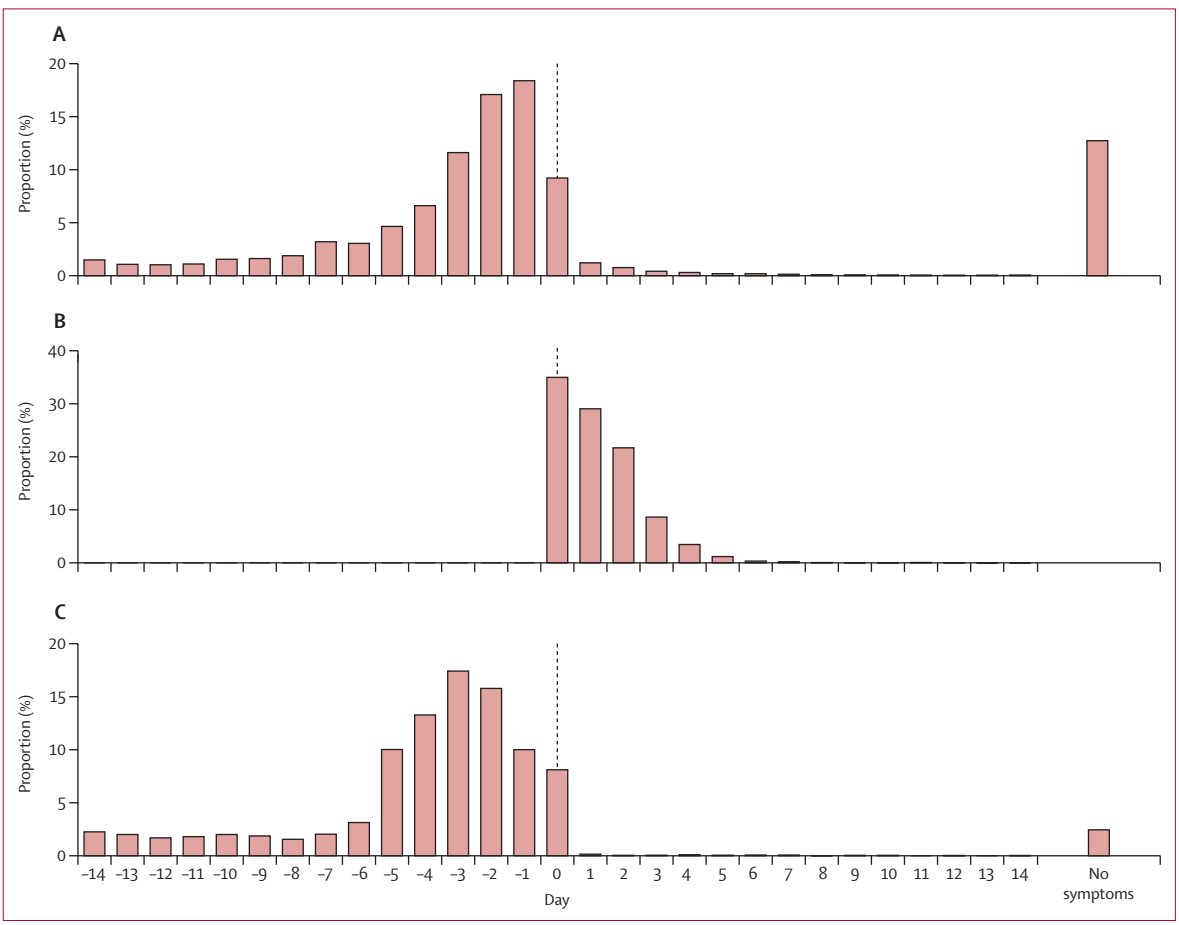

Figure 1: **Timing of symptom onset (A) and nirmatrelvir–ritonavir dispensing (B) relative to date of SARS-CoV-2 testing, and timing of symptom onset relative to data of nirmatrelvir–ritonavir dispensing (C)**
In (A) and (B), day 0 was the date of the index positive test for SARS-CoV-2, whereas in (C) day 0 was the date when nirmatrelvir–ritonavir was dispensed. Our analyses include only recipients of nirmatrelvir–ritonavir who received a positive outpatient PCR test for SARS-CoV-2.

nirmatrelvir–ritonavir because they were at high risk of COVID-19 progression as defined in US Emergency Use Authorization guidelines.[25] To understand the potential association of the timing of treatment initiation with clinical outcomes, we did exploratory analyses within subgroups, including people treated 0–3 days after symptom onset (the primary exposure assessed in the EPIC-HR trial[3]), people treated 6 or more days after symptom onset or in the absence of documented acute COVID-19 symptoms, and people treated at any time after symptom onset. As an additional exploratory analysis intended to emulate the design of the EPIC-HR trial, in which people with COVID-19 were randomly assigned to receive nirmatrelvir–ritonavir or placebo at the point of testing, we distinguished courses dispensed on the day of testing by censoring observations from people who received treatment at later timepoints. We did all analyses in R (version 4.2.1).

Role of the funding source

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

Results

During the study period, 197 484 people without a previous positive test within 90 days tested positive for SARS-CoV-2 infection, of whom 166 980 (84·6%) were eligible for inclusion (appendix pp 4–5). Within this population, 12 574 (7·5%) people received nirmatrelvir–ritonavir at any point in their clinical course. 10 038 (79·8%) nirmatrelvir–ritonavir recipients were tested within 5 days of symptom onset, 1755 (14·0%) were tested 6 or more days after symptom onset, and 781 (6·2%) did not have acute COVID-19 symptoms at the point of testing (figure 1).

Compared with non-recipients, recipients of nirmatrelvir–ritonavir were generally older (7582 [60·3%] recipients were aged 60 years or older, compared with 44 500 [28·8%] of 154 406 non-recipients), and were more likely to have chronic comorbid conditions (7237 [57·6%] *vs* 43 314 [28·1%]; appendix p 6), obesity (5604 [44·6%] *vs* 50 544 [32·7%]), attended an emergency department or been admitted to hospital at least once within the previous year (5115 [40·7%] *vs* 37 407 [24·2%]), and received at least two doses of COVID-19 vaccine (11 411 [90·8%] *vs* 128 090 [83·0%]; 932 [7·4%] recipients had not had any COVID-19 vaccines, compared with 22 338 [14·5%]

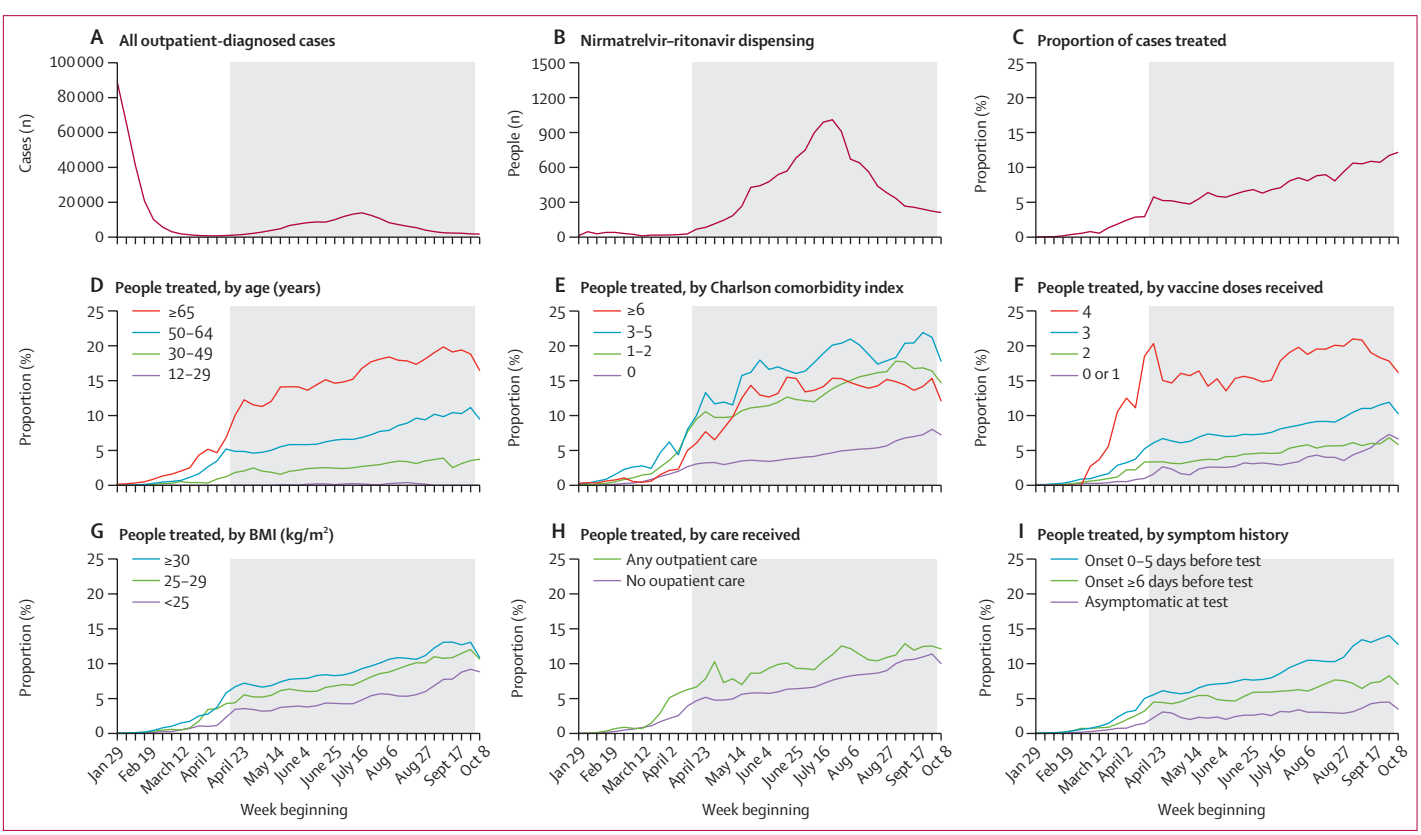

Figure 2: **Receipt of nirmatrelvir–ritonavir among outpatients with COVID-19 over time and according to risk factors**
(A) Total new-onset positive cases of SARS-CoV-2 identified via PCR testing in outpatient settings. (B) Number of people receiving nirmatrelvir–ritonavir. Proportion of people receiving oral nirmatrelvir–ritonavir overall (C), by age group (D), Charlson comorbidity index (E), number of vaccine doses received (F), BMI (G), receipt of outpatient clinical care in association with testing (H), and presence and timing of COVID-19 symptoms at point of testing (I). The data presented are from 2022. People are indexed according to the date of their index positive test for SARS-CoV-2. Shaded areas show the testing dates for which people were included in the study. Trend lines in D–I are 3-week moving averages incorporating data from 7 days before and after each study week.

	Received nirmatrelvir–ritonavir (n=7274)	Did not receive nirmatrelvir–ritonavir (n=126 152)
Age, years*		
12–19	11 (0·2%)	11 054 (8·8%)
20–29	170 (2·3%)	13 047 (10·3%)
30–39	505 (6·9%)	20 761 (16·5%)
40–49	1103 (15·2%)	26 122 (20·7%)
50–59	1556 (21·4%)	23 742 (18·8%)
60–69	1674 (23·0%)	18 117 (14·4%)
70–79	1503 (20·7%)	9213 (7·3%)
80–89	602 (8·3%)	3325 (2·6%)
≥90	150 (2·1%)	770 (0·6%)
Sex		
Female	4196 (57·7%)	69 795 (55·3%)
Male	3080 (42·3%)	56 357 (44·7%)
Time from symptom onset to testing, days		
0–5	5472 (75·2%)	84 657 (67·1%)
6–14	1290 (17·7%)	20 070 (15·9%)
Median (IQR)	2 (1–4)	2 (1–4)
No acute symptoms at point of testing	512 (7·0%)	21 425 (17·0%)
Outpatient or virtual care in association with testing†		
Any care within 1 day before testing	209 (2·9%)	1743 (1·4%)
Any care 1–7 days after testing	3855 (53·0%)	26 639 (21·1%)
Charlson comorbidity index		
0	3740 (51·4%)	99 516 (78·9%)
1–2	2728 (37·5%)	22 055 (17·5%)
3–5	634 (8·7%)	3434 (2·7%)
≥6	172 (2·4%)	1147 (0·9%)
Outpatient visits in previous year		
0	28 (0·4%)	4412 (3·5%)
1–4	776 (10·7%)	34 057 (27·0%)
5–9	1700 (23·4%)	35 836 (28·4%)
10–14	1415 (19·5%)	20 027 (15·9%)
15–19	1043 (14·3%)	11 089 (8·8%)
20–29	1164 (16·0%)	11 495 (9·1%)
30–39	486 (6·7%)	4445 (3·5%)
≥40	662 (9·1%)	4791 (3·8%)

(Table 1 continues in next column)

	Received nirmatrelvir–ritonavir (n=7274)	Did not receive nirmatrelvir–ritonavir (n=126 152)
(Continued from previous column)		
Any emergency department attendance	2279 (31·3%)	20 047 (15·9%)
Any inpatient admission	412 (5·7%)	5663 (4·5%)
Previous SARS-CoV-2 infection†	176 (2·4%)	5540 (4·4%)
COVID-19 vaccine doses received		
0	394 (5·4%)	16 759 (13·3%)
1	49 (0·7%)	2016 (1·6%)
2	965 (13·3%)	31 504 (25·0%)
3	4433 (60·9%)	66 738 (52·9%)
4	1433 (19·7%)	9135 (7·2%)
Race		
White, non-Hispanic	1921 (26·4%)	26 884 (21·3%)
Black, non-Hispanic	688 (9·5%)	9981 (7·9%)
Hispanic	3061 (42·1%)	60 249 (47·8%)
Asian	1225 (16·8%)	18 889 (15·0%)
Pacific Islander	74 (1·0%)	1247 (1·0%)
Other, unknown, or mixed race	305 (4·2%)	8902 (7·1%)
BMI, kg/m²*		
<18·5	38 (0·5%)	5663 (4·5%)
18·5–24·9	1240 (17·0%)	26 550 (21·0%)
25·0–29·9	2190 (30·1%)	33 131 (26·3%)
30·0–39·9	2703 (37·2%)	33 418 (26·5%)
≥40·0	550 (7·6%)	6064 (4·8%)
Smoking status*‡		
Current smoker	254 (3·5%)	4105 (3·3%)
Former smoker	1474 (20·3%)	16 491 (13·1%)
Never smoked	4993 (68·6%)	83 486 (66·2%)
Neighbourhood deprivation index*‡		
First quintile (least deprived)	1235 (17·0%)	17 836 (14·1%)
Second quintile	1667 (22·9%)	27 319 (21·7%)
Third quintile	1825 (25·1%)	31 852 (25·2%)
Fourth quintile	1593 (21·9%)	29 568 (23·4%)
Fifth quintile (most deprived)	948 (13·0%)	19 483 (15·4%)

(Table 1 continues in next column)

non-recipients). 921 (7·3%) treatment recipients had in-person or virtual-care appointments (excluding telephone encounters for which diagnostic codes were not submitted and other informal patient–provider interactions) either 1 day before or on the day of testing compared with 7797 (5·0%) of non-recipients. 6991 (55·6%) nirmatrelvir–ritonavir recipients had in-person or virtual-care appointments 1–7 days after testing, compared with 37 009 (24·0%) non-recipients. Among people aged 12–39 years or 40–64 years, the presence of comorbidities and high BMI were associated with greater increases in the likelihood of receiving nirmatrelvir–ritonavir than among older adults (although we did not do formal significance testing for these associations; appendix pp 7–8).

The proportion of people receiving nirmatrelvir–ritonavir increased with time, with particular increases in dispensing between Dec 31, 2021, and April 7, 2022, among people aged 65 years or older, with comorbid conditions, and with obesity. Differences in the likelihood of nirmatrelvir–ritonavir dispensing among these groups became more pronounced for people diagnosed between April 8 and Oct 7, 2022 (figure 2).

7274 (57·8%) of 12 574 eligible nirmatrelvir–ritonavir recipients and 126 152 (81·7%) of 154 406 eligible

	Received nirmatrelvir–ritonavir (n=7274)	Did not receive nirmatrelvir–ritonavir (n=126 152)
(Continued from previous column)		
Other respiratory vaccines‡		
2021–22 seasonal influenza vaccine	5244 (72·1%)	67 952 (53·9%)
Pneumococcal conjugate vaccine	2071 (28·5%)	23 257 (18·4%)
Pneumococcal polysaccharide vaccine	3912 (53·8%)	29 853 (23·7%)
Clinical outcomes		
Any hospital admission within 30 days	46 (0·6%)	641 (0·5%)
Any intensive care unit admission within 60 days	9 (0·1%)	164 (0·1%)
Mechanical ventilation within 60 days	1 (<0·1%)	41 (<0·1%)
Death within 60 days	10 (0·1%)	124 (0·1%)

Data are n (%), unless otherwise specified. Exposure data among treatment recipients and non-recipients are included for all eligible people who were assigned matches. Comparisons to the full eligible case population are in the appendix (pp 4–5). We included only people taking nirmatrelvir–ritonavir who had a positive outpatient PCR test for SARS-CoV-2. Throughout 2022, 36 759 (42·6%) of 86 254 patients in the Kaiser Permanente Southern California health-care system who received nirmatrelvir–ritonavir in outpatient pharmacy settings did not have a positive test result in their medical record within 14 days before or after dispensing. Among 86 254 patients who received nirmatrelvir–ritonavir, 149 (0·2%) had a positive test result 8–14 days before dispensing, 33 675 (39·0%) had a positive test result 1–7 days before dispensing, 13 627 (15·8%) had a positive test result on the day of dispensing, 1397 (1·6%) had a positive test result 1–7 days after dispensing, and 647 (0·8%) had a positive test result 8–14 days after dispensing. *Variables imputed because of missing data for one age observation, 22 623 smoking observations, 21 879 BMI observations, and 100 neighbourhood deprivation index observations; percentages in the table are computed for people with available observations. †Outpatient care received 1 day before or on the day of the index positive SARS-CoV-2 test across emergency departments, urgent care, physician offices, and telehealth. ‡Not included in matching assignments, but controlled for in regression models via covariate adjustment.

Table 1: **Characteristics of the analysis population**

	Discordant sets		Estimated effectiveness (95% CI)	p value (two-sided)
	Outcome observed for recipient, non-recipient censored (n)	Outcome observed for non-recipient, recipient censored (n)		
All-cause hospital admission or death (within 30 days of positive SARS-CoV-2 test)				
Within 5 days of symptom onset	8	11	79·6% (33·9 to 93·8)	0·0080
Any time (regardless of symptoms)	26	23	53·6% (6·6 to 77·0)	0·031
All-cause ICU admission, mechanical ventilation, or death (within 60 days of positive SARS-CoV-2 test)				
Within 5 days of symptom onset	2	7	89·2% (–25·0 to 99·3)	0·075
Any time (regardless of symptoms)	10	11	84·1% (18·8 to 96·9)	0·027

Treatment effectiveness percentages were calculated by subtracting hazard ratios from 1 and multiplying by 100. Time at risk was measured from the date of the index positive test, and individuals' exposure status was updated at the point of treatment. Estimates were fitted via Cox proportional hazards models across each of five pseudo-datasets generated by multiple imputation of missing values. Regression strata included age (±10 years); sex; time from symptom onset or absence of symptoms; receipt of outpatient care in association with testing; Charlson comorbidity index, health-care interactions in the previous year, number of COVID-19 vaccines received at least 14 days before testing, and BMI. Other variables listed in table 1 were controlled for via covariate adjustment. In the appendix we present effectiveness estimates for alternative subgroups defined by time from symptom onset to testing and the presence or absence of symptoms (pp 16–17), and indicate reasons for censoring and length of follow-up (p 11). ICU=intensive care unit.

Table 2: **Effectiveness of nirmatrelvir–ritonavir in preventing progression to severe disease endpoints**

non-recipients were retained in analyses of treatment effectiveness because they had at least one eligible match (table 1; appendix pp 9–10). During follow-up in the overall analytic sample (n=133 426), there were 687 (0·5%) hospital admissions, 173 (0·1%) ICU admissions, 42 (<0·1%) people requiring mechanical ventilation, and 134 (0·1) deaths, compared with 1440 (0·9%), 429 (0·3%), 133 (0·1%), and 423 (0·3%), respectively, in the full eligible population (n=166 980). Differences between recipients and non-recipients of nirmatrelvir–ritonavir within the analytic sample were similar to those within the full eligible population (table 1; appendix pp 4–6, 9–10).

The primary outcome of hospital admission or death from any cause within 30 days from the index test occurred among 51 (0·7%) nimatrelvir–ritonavir recipients and 695 (0·6%) non-recipients (appendix p 11). Disenrolment or censoring before 30 days or before occurrence of the primary endpoint occurred for 212 (2·9%) nimatrelvir–ritonavir recipients and 2790 (2·2%) non-recipients. After adjustment for differences among treated and untreated people, receipt of nirmatrelvir–ritonavir within 5 days of onset of COVID-19 symptoms had an estimated effectiveness of 79·6% (33·9–93·8; p=0·0080) against progression to hospital admission or death due to any cause within 30 days (table 2). Courses of nirmatrelvir–ritonavir at any time, irrespective of the presence or timing of symptoms, had 53·6% (6·6–77·0) effectiveness against progression to the same endpoint. Among people who received nirmatrelvir–ritonavir, those who were admitted to hospital or died within 30 days of their index test seemed more likely to be aged 60 years or older (42 [82%] of 51 *vs* 3887 [53·8%] of 7223), more likely to have been tested 6 days or more after symptom onset (21 [41%] *vs* 1269 [17·6%]), and more likely to have comorbidities (42 [82%] *vs* 3492 [48·3%]; appendix p 12) than those who did not get admitted to hospital or die.

We did not identify significant evidence of protection against the rare outcome of ICU admission, mechanical ventilation, or death within 60 days of the index test for nirmatrelvir-ritonavir courses dispensed within 0–5 days of symptom onset (table 2). For nirmatrelvir–ritonavir dispensed at any time in the clinical course, estimated effectiveness against this endpoint was 84·1% (95% CI 18·8–96·9; p=0·027). Attributes distinguishing people who experienced this secondary endpoint from those who did not resembled the attributes predicting hospital admission or death within 30 days of the index test (appendix p 14).

In subgroup analyses of people who had received at least two doses of COVID-19 vaccine, estimated effectiveness of nirmatrelvir–ritonavir against hospital admission or death within 30 days was 83·1% (95% CI

	Discordant sets		Estimated effectiveness (95% CI)	p value (two-sided)
	Outcome observed for recipient, non-recipient censored	Outcome observed for non-recipient, recipient censored		
No COVID-19 vaccine doses				
Within 5 days of symptom onset	1	0	..	..
Any time (regardless of symptoms)	1	0	..	..
One COVID-19 vaccine dose				
Within 5 days of symptom onset	0	0	..	..
Any time (regardless of symptoms)	1	0	..	..
At least two COVID-19 vaccine doses				
Within 5 days of symptom onset	7	11	83·1% (30·4–95·9)	0·014
Any time (regardless of symptoms)	24	23	55·3% (6·6–78·7)	0·032
At least three COVID-19 vaccine doses				
Within 5 days of symptom onset	6	11	92·2% (52·0–98·7)	0·0059
Any time (regardless of symptoms)	21	22	66·5% (24·0–85·3)	0·0089
Met criteria defining high risk for COVID-19 progression*				
Within 5 days of symptom onset	8	10	81·2% (35·6–94·6)	0·0078
Any time (regardless of symptoms)	26	22	51·6% (2·4–76·0)	0·043

Treatment effectiveness percentages were calculated by subtracting hazard ratios from 1 and multiplying by 100. Time at risk was measured from the date of the index positive test, and individuals' exposure status was updated at the point of treatment. Estimates were fitted via Cox proportional hazards models across each of five pseudo-datasets generated by multiple imputation of missing values. Regression strata included age (±10 years); sex; time from symptom onset or absence of symptoms; receipt of outpatient care in association with testing; Charlson comorbidity index, health-care interactions in the previous year, number of COVID-19 vaccines received at least 14 days before testing, and BMI. Other variables listed in table 1 were controlled for via covariate adjustment. *Per the US Food and Drug Administration Emergency Use Authorization for nirmatrelvir–ritonavir, criteria defining a high risk of COVID-19 progression included age ≥50 years, BMI ≥30 kg/m^2, cigarette smoking, being unvaccinated or undervaccinated (ie, having received two or fewer doses of COVID-19 vaccine), and presence of indicated comorbid conditions, including asthma, cancer, cerebrovascular disease, chronic diseases affecting the kidneys, lungs, liver, or heart, diabetes, disabilities, HIV, immunocompromised or immunosuppressed status (including due to receipt of solid organ transplant), depression or related mood disorders, and dementia or related neurological disorders. In analyses of undervaccinated status in which people who had received two vaccine doses were excluded, the effectiveness of nirmatrelvir–ritonavir among individuals at high risk of COVID-19 progression was 83·4% (95% CI 44·8–95·0; p=0·0034) if dispensed 0–5 days after symptom onset, and 51·6% (4·0–75·6; p=0·038) for treatment courses dispensed at any time.

Table 3: **Effectiveness of nirmatrelvir–ritonavir in preventing progression to hospital admission or death within 30 days of positive SARS-CoV-2 test, by vaccination or risk status**

30·4–95·9; p=0·014) when given within 5 days of symptom onset and 55·3% (6·6–78·7; p=0·032) when given at any time (table 3). In subgroup analyses of people who had received at least three doses of COVID-19 vaccine, estimated effectiveness against the same endpoint was 92·2% (52·0–98·7; p=0·0059) when nirmatrelvir–ritonavir was dispensed within 5 days of symptom onset and and 66·5% (24·0–85·3; p=0·0089) when it was dispensed at any time (table 3). In analyses restricted to people at high risk of COVID-19 progression, nirmatrelvir–ritonavir had estimated effectiveness against hospital admission or death within 30 days of 81·2% (35·6–94·6; p=0·0078) when dispensed within 5 days of symptom onset (similar to the findings of the primary analysis) and effectiveness of 51·6% (2·4–76·0; p=0·043) when dispensed at any time (table 3).

In exploratory analyses, nirmatrelvir–ritonavir was associated with estimated effectiveness of 89·6% (95% CI 50·2–97·8; p=0·0045) against hospitalisation or death for people who received treatment on the day of their index test and within 5 days of symptom onset (appendix p 16). For all people dispensed nirmatrelvir–ritonavir on the day of their index test, effectiveness against the same endpoint was 77·7% (31·3–92·7; p=0·0083). Further data about the relation between timing of dispensing, onset of symptoms, and the effectiveness of nirmatrelvir–ritonavir are in the appendix (p 17). People tested and treated at later stages in the clinical course of their COVID-19 illness were generally older, more likely to receive outpatient care in association with testing, and more likely to have chronic comorbid conditions than those tested or treated within 0–5 days of symptom onset (appendix pp 18–23).

Discussion

In this retrospective cohort study in a highly vaccinated US outpatient population, receiving nirmatrelvir–ritonavir effectively reduced the incidence of hospitalisation or death within 30 days of a positive test for SARS-CoV-2 compared with not receiving nirmatrelvir–ritonavir. Early treatment was associated with the greatest clinical benefit: when dispensed within 5 days of symptom onset nirmatrelvir–ritonavir was associated with estimated effectiveness of 79·6% (95% CI 33·9–93·8) against this endpoint. Overall, our findings suggest that early receipt of nirmatrelvir–ritonavir (ie, within 5 days of symptom onset) reduces risk of hospital admission or death in people testing positive for SARS-CoV-2 in outpatient settings, underscoring the continued need for prompt testing and treatment among people at high risk of progression to severe COVID-19.

Post-licensing studies[4–10] of nirmatrelvir–ritonavir effectiveness in Israel, Hong Kong, and the USA have had discordant results in terms of effectiveness against severe disease and hospital admission in outpatients. Studies done during the initial roll-out of nirmatrelvir–ritonavir generally enrolled populations at high risk of disease progression: for instance, in two studies[4,6] done in Israel, the mean age of treated cases was 67–69 years, and the prevalence of obesity, diabetes, hypertension, and cardiovascular disease among treated cases exceeded 30% in each study. Consistent with our findings, older age and comorbidities predicted increased risk of the primary outcome (COVID-19-related hospital admission) in these studies.[4,6] In one of these studies,[4] the estimated effectiveness of nirmatrelvir–ritonavir was greater among adults aged 65 years or older than among those aged 40–64 years, and among adults who had received at least two doses of COVID-19 vaccine or experienced previous natural infection than among those without previous immunity. However, such patterns are inconsistent across reports. In a US study,[5] nirmatrelvir–ritonavir had greater effectiveness among adults younger

than 65 years than among those aged 65 years or older, while in another US study[10] and a study in Hong Kong[8] effectiveness did not seem to differ by age, immunity, or the presence of comorbidities. Studies in Hong Kong,[7,8] in which the oldest study populations (most treated cases aged >70 years) with the lowest vaccine coverage (33–42% fully vaccinated against COVID-19) have been enrolled, have generated the lowest estimates of the effectiveness of nirmatrelvir–ritonavir (21–33%). However, differences across settings or over time in hospital admission criteria for people with COVID-19 could also contribute to variation in effectiveness estimates.

The perceived risk of progression to severe COVID-19 probably factors into clinical decision making around prescription of nirmatrelvir–ritonavir and treatment adherence, underscoring the need to control for differences in clinical status among people who receive or do not receive treatment in observational studies. Whereas we identify time from symptom onset to dispensing of treatment as a potential modifier of treatment effectiveness, symptoms data were unavailable in previous observational studies for all[4–8,10] or most[9] cases of COVID-19 analysed. Our estimate of 53·6% effectiveness for nirmatrelvir–ritonavir in preventing hospitalisation or death within 30 days for people treated at any time in their clinical course aligns with estimates of 45–51% effectiveness against hospitalisation in other US observational studies[5,10] in which symptoms data were not recorded and analytic samples were not restricted according to the timing of symptom onset. Other unique features of our data might also have helped to control for differences in clinical status and health-care-seeking behaviour in our study, such as the ability to match cases according to whether they received clinical care in association with testing (a potential proxy for disease severity) and the availability of comprehensive data for health-care-seeking behaviour (including outpatient, inpatient, and emergency care) in the past year and receipt of other vaccines, including 2021–22 seasonal influenza vaccination. Matching of multiple patient characteristics enabled us to account for potential interactions among factors associated with risk of severe COVID-19 and the likelihood of being prescribed nirmatrelvir–ritonavir, whereas covariate adjustment and inverse probability weighting strategies might have offered less flexibility.

However, our study also has limitations. First, capture of several variables was incomplete within our data, and potential misclassification of immunity due to undiagnosed previous SARS-CoV-2 infections or those never reported to KPSC remains a concern. Second, unmeasured confounding could have hindered causal inference, although our data included more comprehensive measures of clinical status and health-care-seeking behaviour than those available in previous studies.[4–10] Other antivirals and monoclonal antibody therapies were rarely prescribed in our sample, but would probably have reduced the effectiveness of nirmatrelvir–ritonavir compared with not receiving nirmatrelvir–ritonavir, because these treatments were prioritised for patients who could not receive nirmatrelvir–ritonavir because of potential drug interactions. Third, we cannot verify whether people who received nirmatrelvir–ritonavir adhered to treatment as recommended. Our findings should thus be interpreted as measuring intention-to-treat effects under real-world conditions of use. Fourth, our approach to variable selection via a directed acyclic graph, and use of matching to accommodate potential interactions among confounding variables, prioritised validity over precision of estimates, resulting in wide confidence intervals. A fifth and related concern is that, because of the low risk of severe disease within our highly vaccinated study population, the primary and secondary endpoints occurred rarely among both treatment recipients and non-recipients, further limiting the precision of our estimates and our ability to explore effect modification. Concerns about sparse data bias are partly mitigated by the fact that variation in effectiveness estimates was consistently associated with timing of treatment dispensing, and that our effectiveness estimates shortly after symptom onset closely mirrored findings of the EPIC-HR trial.[3] Sixth, our endpoint of hospital admission or death due to any cause after a positive outpatient SARS-CoV-2 test might have captured admissions unrelated to COVID-19. If present, misclassification of incidental hospital admissions would be expected to lead to underestimation of the true effect of treatment, especially if a higher proportion of hospital admissions among treated people were incidental.[26,27] Finally, the adjusted hazard ratios used to calculate effectiveness could have been affected by underlying depletion-of-susceptibles bias, whereby rapid progression to hospital admission among people at the greatest risk might have contributed to changes over time in the distribution of covariates among treated and untreated people.

Expanding availability of home-based antigen testing might have altered patient demand for clinic-based PCR testing during the study period. Patients who underwent PCR testing might have had more severe symptoms than those who did not seek clinic-based testing. Conversely, infections captured by clinic-based testing (including screening for travel or medical procedures) might have over-represented asymptomatic or paucisymptomatic infections, because people with substantial symptoms might have resorted primarily to at-home antigen testing. Restricting our analyses to people who underwent clinic-based testing might have helped to mitigate differences in health-care-seeking behaviour under either of these scenarios and provided a basis for comparing outcomes among recipients and non-recipients with known infection status and history of symptoms. However, our findings might not be generalisable to patients tested for SARS-CoV-2 infection outside clinical settings.

Vaccination has been highly effective in preventing severe outcomes of SARS-CoV-2 infection and mitigating the burden of COVID-19 within populations. Although risks of severe COVID-19 have thus been reduced substantially, outcomes such as hospital admission and death remain of concern for some vaccinated populations, including older adults and those with chronic underlying medical conditions. Our findings suggest that timely dispensing of nirmatrelvir–ritonavir could reduce individuals' risk of hospitalisation or death within 30 days. Further research is warranted to establish the potential value of nirmatrelvir–ritonavir in preventing additional endpoints, including post-COVID-19 condition, as longer follow-up of treated patients becomes possible.

Contributors

JAL, JMM, DM, and SYT conceived the study and wrote the first draft of the Article. JAL and VH did the analysis. All authors contributed to study design, edited the Article for important intellectual content, and gave final approval of the version to be published. All authors had full access to all the data and had final responsibility for the decision to submit for publication. JAL and VH verified all the data.

Declaration of interests

JAL has received grants and consultancy fees from Pfizer. SYT has received grants from Pfizer. LP, LJ, and JMM are employees of Pfizer, and hold stock and stock options in Pfizer.

Data sharing

Anonymised data that support the findings of this study might be made available by the investigative team if the inquirers agree to collaborate with the study team on all publications, provide external funding for the administrative and investigator time necessary for this collaboration, show that they are qualified and have documented evidence of training for human participant protections, and agree to abide by the terms outlined in data-use agreements between institutions.

Acknowledgments

This study was funded by the US Centers for Disease Control and Prevention (grant 75D3-121C11520 to SYT) and the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health (grant R01-AI4812701A1 to JAL).

References

1 US National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. 2021. http://www.ncbi.nlm.nih.gov/books/NBK570371/ (accessed Jan 20, 2023).
2 Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. *Nature* 2022; **604:** 553–56.
3 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.
4 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.
5 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).
6 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; **76:** e342–49.
7 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet* 2022; **400:** 1213–22.
8 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; **76:** e26–33.
9 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalized 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.
10 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.
11 Vasan A, Foote M, Long T. Ensuring widespread and equitable access to treatments for COVID-19. *JAMA* 2022; **328:** 705–06.
12 Bajema KL, Wang XQ, Hynes DM, et al. Early adoption of anti-SARS-CoV-2 pharmacotherapies among US veterans with mild to moderate COVID-19, January and February 2022. *JAMA Netw Open* 2022; **5:** e2241434.
13 Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of infection-induced SARS-CoV-2 antibodies—United States, September 2021–February 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 606–08.
14 Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes associated with SARS-CoV-2 omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California. *Nat Med* 2022; **28:** 1933–43.
15 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.
16 Andrejko KL, Myers JF, Fukui N, et al. Real-world uptake of COVID-19 vaccination among individuals expressing vaccine hesitancy: a registry-linkage study. *medRxiv* 2022; published online Aug 3. https://doi.org/10.1101/2022.08.02.22278300 (preprint).
17 Malden DE, Tartof SY, Ackerson BK, et al. Natural language processing for improved COVID-19 characterization: evidence from more than 350,000 patients in a large integrated health care system. *JMIR Public Health Surveill* 2022; **8:** e41529.
18 Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health* 2006; **83:** 1041–62.
19 Sundarajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004; **57:** 1288–94.
20 Huynh DN, Millan A, Quijada E, John D, Khan S, Funahashi T. Description and early results of the Kaiser Permanente Southern California COVID-19 home monitoring program. *Permanente J* 2021; **25:** 1–7.
21 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; **69:** 239–41.
22 Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. *Ann Intern Med* 2020; **173:** 773–81.
23 Fernández Villalobos NV, Ott JJ, Klett-Tammen CJ, et al. Effect modification of the association between comorbidities and severe course of COVID-19 disease by age of study participants: a systematic review and meta-analysis. *Syst Rev* 2021; **10:** 194.
24 Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996; **91:** 473–89.
25 US Food and Drug Administration. Emergency Use Authorization (EUA) of Paxlovid for coronavirus disease 2019 (COVID-19). https://www.fda.gov/media/155051/download (accessed Jan 20, 2023).
26 Lewnard JA, Patel MM, Jewell NP, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. *Epidemiology* 2021; **32:** 508–17.
27 Stowe J, Andrews N, Kirsebom F, Ramsay M, Lopez Bernal J. Effectiveness of COVID-19 vaccines against omicron and delta hospitalization: a test-negative case-control study. *Nat Comm* 2022; **13:** 5736.