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Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study

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Summary

Background Data on the effectiveness of oral antivirals in patients with mild-to-moderate COVID-19 are urgently needed. This retrospective cohort study aimed to evaluate the clinical and virological outcomes associated with molnupiravir or nirmatrelvir–ritonavir use in hospitalised patients with mild-to-moderate COVID-19 during a pandemic wave dominated by the omicron BA.2 subvariant.

Methods We analysed data from a territory-wide retrospective cohort of patients in Hong Kong who were hospitalised with a confirmed diagnosis of SARS-CoV-2 infection between Feb 26 and April 26, 2022. Data were extracted from the Hospital Authority, the Department of Health, and the Hong Kong Death Registry. Patients were eligible for inclusion if their admission date was within 3 days before or after confirmation of their COVID-19 diagnosis. Those who were admitted to hospital more than 5 days after symptom onset, were younger than 18 years, had a history of oral antiviral use before admission, required supplemental oxygen on admission, had drug-related contraindications to nirmatrelvir–ritonavir use, or had severe renal or severe liver impairment were excluded. Patients who received the oral antivirals molnupiravir or nirmatrelvir–ritonavir were matched with controls using propensity-score matching in a ratio of 1:1. The primary outcome was all-cause mortality and secondary outcomes included a composite outcome of disease progression (all-cause mortality, initiation of invasive mechanical ventilation [IMV], intensive care unit [ICU] admission, or the need for oxygen therapy) and each of these individual disease progression outcomes, and time to reaching a low viral burden (RT-PCR cycle threshold value ≥30). For each event outcome, crude incidence rates were calculated and hazard ratios (HRs) estimated using Cox regression models.

Findings We identified 40 776 patients hospitalised with SARS-CoV-2 infection during the study period, with a mean follow-up of 41·3 days (total 925 713 person-days). After exclusions and propensity-score matching, we included 1856 molnupiravir recipients and 1856 matched controls, and 890 nirmatrelvir-ritonavir recipients and 890 matched controls. A lower risk of all-cause mortality was observed in molnupiravir recipients (crude incidence rate per 10 000 person-days 19·98 events [95% CI 16·91–23·45]) versus matched controls (38·07 events [33·85–42·67]; HR 0·48 [95% CI 0·40–0·59], p<0·0001) and in nirmatrelvir–ritonavir recipients (10·28 events [7·03–14·51]) versus matched controls (26·47 events [21·34–32·46]; HR 0·34 [0·23–0·50], p<0·0001). Oral antiviral recipients also had lower risks of the composite disease progression outcome (molnupiravir HR 0·60 [95% CI 0·52–0·69], p<0·0001; nirmatrelvir–ritonavir 0·57 [0·45–0·72], p<0·0001) and need for oxygen therapy (molnupiravir 0·69 [0·57–0·83], p=0·0001; nirmatrelvir–ritonavir 0·73 [0·54–0·97], p=0·032) compared with controls. Time to achieving a low viral burden was significantly shorter among oral antiviral recipients than matched controls (molnupiravir HR 1·38 [95% CI 1·15–1·64], p=0·0005; nirmatrelvir–ritonavir 1·38 [1·07–1·79], p=0·013). Significant differences in initiation of IMV and ICU admission were not found.

Interpretation During a wave of SARS-CoV-2 omicron BA.2, initiation of novel oral antiviral treatments in hospitalised patients not requiring oxygen therapy on admission showed substantial clinical benefit. Our findings support the early use of oral antivirals in this population of patients.

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For the Chinese translation of the abstract see **online** for appendix 1

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Introduction

During the COVID-19 pandemic, various drugs have been repurposed or developed for treating patients with SARS-CoV-2 infection. In December, 2021, molnupiravir and ritonavir-boosted nirmatrelvir, two oral antivirals, were granted emergency use authorisation by the US Food and Drug Administration for the treatment of non-hospitalised patients with mild-to-moderate

Research in context

Evidence before this study

The medical and research community are actively exploring the use of oral antivirals in patients with COVID-19 to lower their risks of hospitalisation and death and to reduce the burden on health-care systems. We searched Scopus and PubMed for studies published from database inception until May 13, 2022, using the search terms "SARS-CoV-2 OR COVID-19" AND "molnupiravir OR Lagevrio OR EIDD-2801" OR "nirmatrelvir OR Paxlovid OR PF-07321332", without language restrictions. Major studies examining the safety and efficacy of molnupiravir include MOVe-IN and MOVe-OUT trials conducted in hospitalised and non-hospitalised patients with COVID-19, respectively. Clinical evidence for the use of ritonavir-boosted nirmatrelvir came from the EPIC-HR trial of non-hospitalised adults with COVID-19. Although no clinical benefits have been observed with molnupiravir use in the inpatient setting in patients with moderate-to-severe COVID-19, early initiation of molnupiravir or nirmatrelvir–ritonavir within 5 days of symptom onset in non-hospitalised patients with mild-to-moderate COVID-19 and risk factors for progression to severe disease has been associated with relative risk reductions in the combined outcome of hospitalisation or death (30% for molnupiravir and 88% for nirmatrelvir–ritonavir). Notably, these clinical trials were conducted before the omicron variant became prevalent, and the efficacy of oral antivirals against this variant of concern could until now only be inferred from experimental evidence. Real-world evidence of oral antiviral use in patients infected with the SARS-CoV-2 omicron variant is insufficient.

Added value of this study

To the best of our knowledge, this is the first real-world study to explore the inpatient use of oral antivirals during a pandemic wave dominated by the SARS-CoV-2 omicron variant. We conducted a territory-wide, retrospective cohort study to examine the effectiveness of molnupiravir or nirmatrelvir–ritonavir in patients with COVID-19 who did not require supplemental oxygen on admission to hospital in Hong Kong. Early initiation of oral antivirals within 2 days of admission was associated with significantly lower risks of all-cause mortality and disease progression, and with reaching a low viral burden faster than their respective matched controls. Receipt of oral antivirals was also associated with a reduced need for oxygen therapy than non-receipt.

Implications of all the available evidence

Current guidelines are now prioritising the distribution of oral antivirals to those who do not require supplemental oxygen but who are at the highest risk of disease progression. Our study cohort reflected such a prescription pattern in real-world clinical practice, consisting of mostly older people with multiple pre-existing comorbidities and who had not been fully vaccinated. The antiviral effect and mortality benefit observed in this patient cohort support the use of oral antivirals in patients with COVID-19 who do not require supplemental oxygen on admission during a pandemic wave of the omicron variant. Ongoing research will inform the safety and effectiveness of oral antivirals in specific patient populations (by vaccination status and viral variant), drug combinations, and different health-care settings.

COVID-19 who are at risk of progression to severe disease, so as to reduce the burden on health-care systems by lowering the risk of hospitalisation or death in these patients.[1,2]

Although both molnupiravir and nirmatrelvir–ritonavir are indicated for these patients within 5 days of symptom onset, current guidelines prioritise the use of nirmatrelvir–ritonavir (relative risk reduction 88%) or another antiviral, remdesivir (87%), which have shown higher efficacy than molnupiravir (30%) in reducing hospitalisation or death among patients with COVID-19 who do not require hospitalisation or supplemental oxygen.[1–4] Notably, several concerns and research gaps remain with regard to the use of molnupiravir and nirmatrelvir–ritonavir, such as whether initiation in patients with asymptomatic COVID-19 is appropriate, the need for more clinical data on the treatment of patients infected with specific variants of concern, and the safety and efficacy of these drugs in vaccinated individuals with breakthrough infections.[5–7] Furthermore, the efficacy of molnupiravir, as illustrated in the MOVe-OUT trial, has been questioned because of the trial's premature termination, imbalances in risk factors and COVID-19 severity of patients at baseline, results with borderline statistical significance and of uncertain clinical significance, and discrepancies between interim and full analyses that could not be fully explained by differences in patient characteristics.[8–10]

Real-world evidence of the effectiveness of molnupiravir and nirmatrelvir–ritonavir in patients with COVID-19 is urgently needed.[11] In this retrospective cohort study, we aimed to evaluate clinical and virological outcomes following the use of molnupiravir or nirmatrelvir–ritonavir in patients with COVID-19 during a community epidemic in Hong Kong dominated by the omicron BA.2 subvariant of SARS-CoV-2. Although these oral antivirals are now indicated for non-hospitalised patients with COVID-19 who are at high risk of disease progression, the current analysis focuses on their effectiveness in hospitalised patients with COVID-19 who do not initially require any oxygen therapy on admission.

Methods

Study design

We conducted a territory-wide, retrospective cohort study in Hong Kong of hospitalised adult patients with COVID-19 and without oxygen therapy on admission, who were given molnupiravir or nirmatrelvir–ritonavir, during the period from Feb 26 to May 3, 2022.

This study was approved by the institutional review board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (reference number UW 20-493). Given the extraordinary nature of the COVID-19 pandemic, individual patient-informed consent was not required for this retrospective cohort study using anonymised data.

The study protocol is available in appendix 2 (pp 15–19).

Data sources and study population

Electronic health records of patients with COVID-19 were retrieved from the Hospital Authority, a statutory provider of public inpatient services and primary public outpatient services in Hong Kong. Electronic health records include demographic characteristics, date of registered death, and data on hospital admissions, emergency department visits, diagnoses, prescription and drug dispensing records, procedures, and laboratory tests. The Hospital Authority linked the health records with anonymised population-based vaccination records provided by the Centre for Health Protection of the Hong Kong Department of Health using unique identification numbers (Hong Kong Identity Card or foreign passport number). The database has been widely used for studies to evaluate the safety and effectiveness of drug treatments for COVID-19 at the population level.[12,13]

For assessment of all-cause mortality, data were extracted from the Hong Kong Death Registry, which allowed us to capture data on deaths of patients that occurred beyond hospital discharge (outside the hospital setting).

Our cohort comprised patients with positive RT-PCR or rapid antigen test results for SARS-CoV-2 infection who were admitted to isolation wards at local public hospitals between Feb 26 and April 26, 2022. Patients were eligible for inclusion if they had been admitted within 3 days of their COVID-19 diagnosis date, or if a COVID-19 diagnosis was confirmed within 3 days of their admission date, so as to account for any potential time lag in the confirmation of cases during an upsurge of patients with SARS-CoV-2 infection. The index date was defined as the date of hospital admission (day 0). We excluded patients who were admitted to hospital with COVID-19 before Feb 26, 2022 (the date when molnupiravir first became locally available), after April 26, 2022 (less than 1 week of follow-up), or more than 5 days after symptom onset; those younger than 18 years; those with a history of oral antiviral use before admission; and those with oxygen support or mechanical ventilation on the index date. Patients with drug contraindications to nirmatrelvir–ritonavir (ie, use of amiodarone, apalutamide, lumacaftor–ivacaftor, ivosidenib, rifampicin, rifapentine, carbamazepine, St John's Wort, primidone, phenobarbital, or phenytoin in the 6 months before baseline),[14] severe renal impairment[2] (estimated glomerular filtration rate <30 mL/min per 1·73 m², dialysis, or renal transplantation), or severe liver impairment[2] (cirrhosis, hepatocellular carcinoma, or liver transplantation) at baseline were excluded from the analysis to further mitigate confounding by indication as much as possible, and to restrict the sample to those who were as equally eligible to receive either molnupiravir or nirmatrelvir–ritonavir treatment as possible.

Treatment exposure and follow-up

See Online for appendix 2

Hospitalised patients with COVID-19 without oxygen therapy and who received early molnupiravir or nirmatrelvir–ritonavir treatment at public hospitals during the observation period were defined as having treatment exposure. Because all public hospitals in Hong Kong are managed by the Hospital Authority, oral antivirals were prescribed to patients with COVID-19 as clinically appropriate on the basis of the same set of standard treatment protocols, and molnupiravir and nirmatrelvir–ritonavir were equally accessible across all public hospitals during the study period (molnupiravir was available from Feb 26, 2022,[15] and nirmatrelvir–ritonavir was locally available from March 16, 2022).[16] We defined the treatment exposure period as within the first 2 days of admission to mitigate potential immortal time bias between treatment initiation and admission.[17–20] Controls were selected from the cohort of hospitalised patients with COVID-19 without oxygen therapy who did not receive molnupiravir or nirmatrelvir–ritonavir during the observation period, using propensity-score matching in a ratio of 1:1, and considering the time of admission. Patients were observed from the index date until the date of registered death, the occurrence of outcome events, crossover of oral antiviral treatment, or the end of the observation period (May 3, 2022), whichever came first.

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes were a composite outcome of disease progression (all-cause mortality, initiation of invasive mechanical ventilation [IMV], intensive care unit admission, or need for oxygen therapy) and each of these individual disease progression outcomes, and time to reaching a low viral burden (defined as a cycle threshold [Ct] value of 30 or higher on an RT-PCR assay for SARS-CoV-2). Viral burden information at baseline was not necessarily immediately available for a minority of patients who were admitted on the basis of a positive rapid antigen test, and quantitative viral burden was not assessed as a routine procedure, especially during the peak of the omicron BA.2 epidemic when public hospitals were overwhelmed with cases. Length of

hospital stay was also assessed as a prespecified secondary outcome for patients who were discharged alive. In response to an upsurge of COVID-19 cases during the study period and the limited number of hospital beds, the Hospital Authority had revised their discharge criteria on Feb 26, 2022, to allow patients hospitalised with COVID-19 to be discharged as soon as they were deemed clinically stable by their attending physicians. Discharge was conditional on the patient's residential premises being suitable for isolation or the patient being accepted by community isolation facilities, where they would continue their isolation until negative test results were obtained (on days 6 and 7 for individuals vaccinated with at least two doses and on day 14 for those unvaccinated or vaccinated with only one dose).[21]

Over the follow-up period, changes in the proportion of patients with each clinical status (in-hospital death, on IMV, not on IMV, and discharged) were compared between each oral antiviral group and the respective control group.

Baseline covariates

Baseline covariates of patients included age, sex, region of residence, nursing home residence (yes or no), symptom onset date reported (yes or no), date of hospital admission, nosocomial infection (yes or no; defined as hospitalisation before COVID-19 diagnosis), time period of hospital admission (Feb 26 to March 31, 2022, or April 1 to April 26, 2022), Charlson Comorbidity Index, any previous SARS-CoV-2 infection (yes or no; defined as a recorded medical history of confirmed SARS-CoV-2 infection), COVID-19 vaccination status (with fully vaccinated defined as having received at least two doses of Comirnaty [also known as BNT162b2, tozinameran] or three doses of CoronaVac), concomitant treatments initiated on the index date (yes or no for each of antibiotics, dexamethasone or other systemic steroid, interferon-beta-1b, baricitinib, and tocilizumab), and laboratory parameters on admission (Ct value, lactate dehydrogenase concentration, C-reactive protein concentration, and lymphocyte count).

Statistical analysis

We used propensity-score models conditional on the aforementioned baseline covariates without first-order interactions in a logistic regression model, and the propensity of receiving each oral antiviral was estimated in an approach of calliper matching without replacement, with a calliper width of 0·05. Missing laboratory data (appendix 2 p 2) for molnupiravir or nirmatrelvir–ritonavir recipients were imputed 20 times using other data in the propensity-score model.[22] We applied Rubin's rules to pool the treatment effects estimated from the 20 independent imputed datasets.[23] We used the standardised mean difference (SMD) to assess the balance of each baseline covariate between the groups before and after propensity-score matching, with an SMD greater than 0·1 indicating covariate imbalance.[24]

Hazard ratios (HRs) with 95% CIs for each outcome between molnupiravir or nirmatrelvir–ritonavir recipients and non-recipients were estimated using Cox regression models. Because Schoenfeld residuals showed no evidence that the proportional hazards assumption had been violated, we assumed proportionality of HRs in the primary analysis. A cluster-robust sandwich variance–covariance estimator was used in all Cox regression models to account for the correlation within the propensity-score match. Mean differences (95% CIs) for the length of hospital stay endpoint were calculated using linear regression. Analyses were done among the following patient subgroups: age (≤65 or >65 years), fully vaccinated or not, region of residence, study period (before March 16, 2022; or from March 16, 2022, onwards, the date from which both oral antivirals were available across public hospitals), and with and without symptom onset date reported. Sensitivity analyses were done first by including only patients with complete 28-day follow-up (ie, inclusion period from Feb 26 to April 7, 2022), and second by using the observed baseline characteristics without laboratory data (without multiple imputation) for the propensity-score model. We rematched baseline covariates and constructed a new propensity-score model for each subgroup and sensitivity analysis.

All statistical analyses were done with Stata version 17. All significance tests were two-tailed, and $p<0·05$ was considered to indicate statistical significance.

Role of the funding source

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

Results

We identified 40776 patients with a confirmed diagnosis of SARS-CoV-2 infection who were admitted to hospital between Feb 26 and April 26, 2022, with a mean follow-up of 41·3 days (SD 18·7) and a total of 925713 person-days of follow-up. 1880 molnupiravir recipients, 924 nirmatrelvir–ritonavir recipients, and 14810 controls, who had no requirement for oxygen therapy at baseline, were eligible for inclusion (figure 1). Baseline characteristics of the molnupiravir, nirmatrelvir–ritonavir, and control groups before 1:1 propensity-score matching are presented in table 1. After matching, our analysis included 1856 molnupiravir recipients (with 1856 matched controls) and 890 nirmatrelvir–ritonavir recipients (with 890 matched controls); the propensity-score distributions of the oral antiviral groups and matched control groups were highly overlapping (appendix 2 p 13), and the baseline characteristics of patients were balanced between the oral

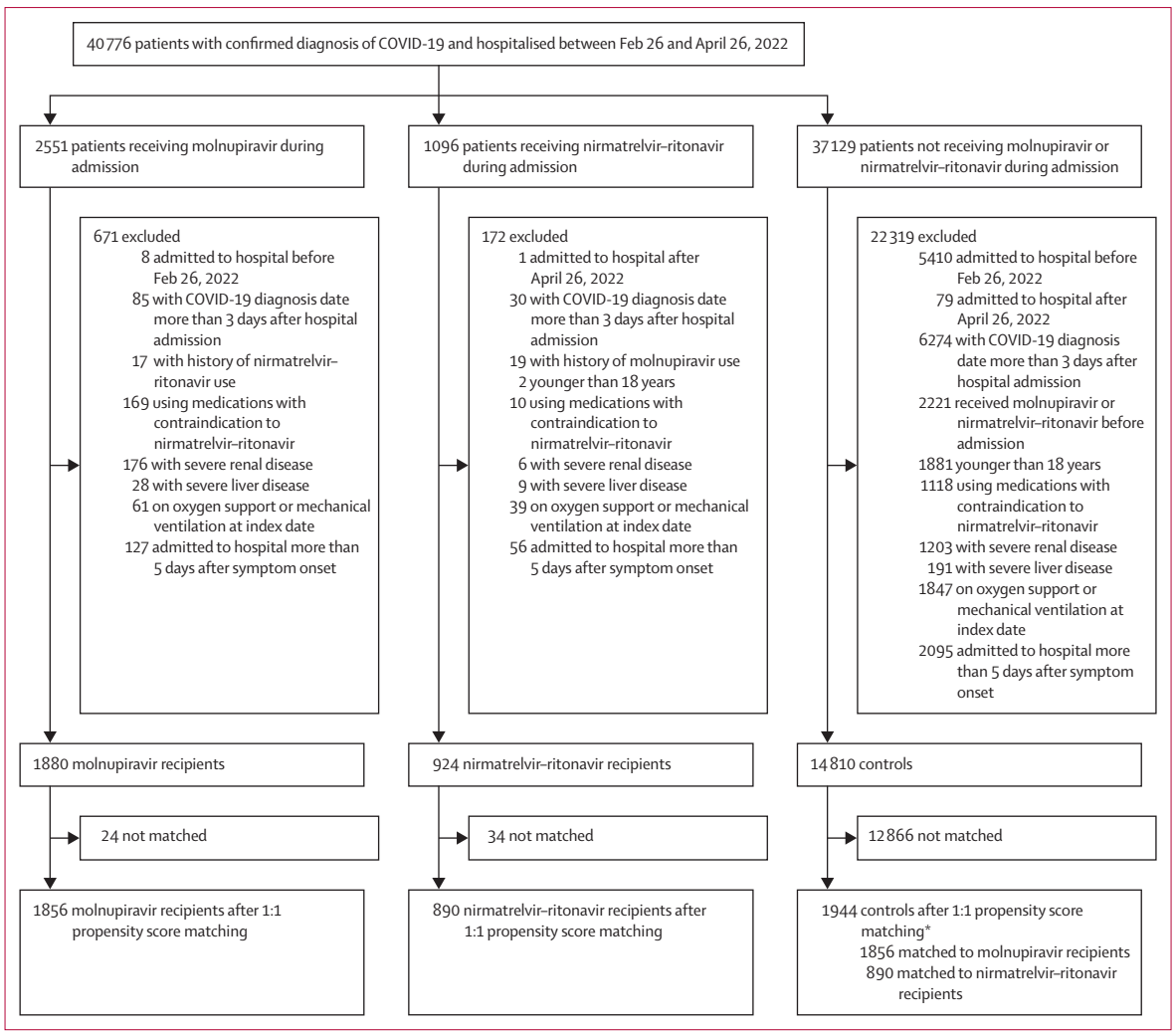

Figure 1: **Identification of molnupiravir recipients, nirmatrelvir–ritonavir recipients, and their matched controls among patients hospitalised with COVID-19 during the study period**

*802 controls were matched to both treatment groups.

antiviral and matched control groups, with SMDs of 0·1 or lower (table 1; appendix 2 pp 3–4). The median duration from symptom onset to molnupiravir initiation was 1 day (IQR 1–3), and that from symptom onset to nirmatrelvir–ritonavir initiation was 1 day (1–3). 1795 (96·7%) molnupiravir recipients received 800 mg molnupiravir twice per day for 5 days, and 880 (98·9%) nirmatrelvir–ritonavir recipients completed the 5 day regimen of 300 mg nirmatrelvir and 100 mg ritonavir twice per day.

The crude incidence rates of all-cause mortality were 19·98 events per 10 000 person-days among molnupiravir recipients (table 2) and 10·28 events per 10 000 person-days among nirmatrelvir–ritonavir recipients (table 3). Receipt of molnupiravir or nirmatrelvir–ritonavir was associated with significantly lower risks of all-cause mortality and the composite disease progression outcome compared with non-receipt, and with a reduced need for oxygen therapy (tables 2, 3; figure 2). The risks of IMV initiation in oral antiviral recipients were not significantly different from that in their control counterparts.

Time to achieving low viral burden (Ct ≥30) was significantly shorter among oral antiviral recipients than matched controls. There was a significant increase in the Ct value between baseline and days 5–7 in the molnupiravir group (mean increase 6·67 cycles [95% CI 5·91–7·43], p<0·0001), the nirmatrelvir–ritonavir group (7·25 cycles [5·93–8·56], p<0·0001), and the control group (3·93 cycles [3·57–4·28], p<0·0001). Compared with the respective matched controls, larger increases in Ct value by days 5–7 were observed in molnupiravir recipients (mean difference 2·50 [95% CI 1·34–3·66], p<0·0001) and nirmatrelvir–ritonavir recipients (2·86 [0·96–4·76], p=0·0034).

Among patients who were discharged alive, no significant differences in length of hospital stay were

	Before 1:1 propensity-score matching					After 1:1 propensity-score matching: standardised mean difference*	
	Molnupiravir recipients (n=1880)	Nirmatrelvir–ritonavir recipients (n=924)	Controls (n=14 810)	Standardised mean difference		Molnupiravir recipients *vs* controls	Nirmatrelvir–ritonavir recipients *vs* controls
				Molnupiravir recipients *vs* controls	Nirmatrelvir–ritonavir recipients *vs* controls		
Age, years							
Mean	80·8 (13·0)	77·2 (14·1)	74·3 (18·7)	0·36	0·16	0·04	0·05
By category	..	..	..	0·40	0·26	0·10	0·07
18–40	27 (1·4%)	29 (3·1%)	1313 (8·9%)	..	..	..	..
41–65	207 (11·0%)	132 (14·3%)	2474 (16·7%)	..	..	..	..
>65	1646 (87·6%)	763 (82·6%)	11 023 (74·4%)	..	..	..	..
Sex	..	..	..	0·03	0·01	0·02	0·02
Male	925 (49·2%)	462 (50·0%)	7500 (50·6%)	..	..	..	..
Female	955 (50·8%)	462 (50·0%)	7310 (49·4%)	..	..	..	..
Region of residence	..	..	..	0·29	0·13	0·05	0·07
Hong Kong Island	502 (26·7%)	187 (20·2%)	2297 (15·5%)	..	..	..	..
Kowloon	607 (32·3%)	288 (31·2%)	4978 (33·6%)	..	..	..	..
New Territories	770 (41·0%)	446 (48·3%)	7511 (50·7%)	..	..	..	..
Others	1 (0·1%)	3 (0·3%)	24 (0·2%)	..	..	..	..
Nursing home residence	579 (30·8%)	130 (14·1%)	5003 (33·8%)	0·06	0·47	0·03	0·01
Symptom onset date reported	1008 (53·6%)	404 (43·7%)	5786 (39·1%)	0·29	0·09	0·01	0·03
Time from symptom onset to hospitalisation, days†	..	..	..	0·08	0·09	0·01	0·01
0	394 (39·1%)	160 (39·6%)	2050 (35·4%)	..	..	..	..
1–5	614 (60·9%)	244 (60·4%)	3736 (64·6%)	..	..	..	..
Nosocomial infection	45 (2·4%)	30 (3·2%)	968 (6·5%)	0·20	0·15	0·02	0·02
Time of admission	..	..	..	0·09	0·13	0·06	0·01
Feb 26 to March 31, 2022	1588 (84·5%)	626 (67·7%)	12963 (87·5%)	..	..	..	..
April 1 to April 26, 2022	292 (15·5%)	298 (32·3%)	1847 (12·5%)	..	..	..	..
Charlson's Comorbidity Index							
Mean	5·8 (1·9)	5·1 (1·7)	5·0 (2·4)	0·33	0·03	0·01	0·02
By category	..	..	..	0·25	0·24	0·06	0·09
1–4	459 (24·4%)	312 (33·8%)	5312 (35·9%)	..	..	..	..
5–6	878 (46·7%)	465 (50·3%)	5951 (40·2%)	..	..	..	..
7–14	543 (28·9%)	147 (15·9%)	3547 (24·0%)	..	..	..	..
Previous SARS-CoV-2 infection	0	0	3 (0·0%)	0·02	0·02	NA	NA
Fully vaccinated against SARS-CoV-2‡	116 (6·2%)	97 (10·5%)	1328 (9·0%)	0·11	0·05	0·00	0·03
Concomitant treatments initiated at admission							
Antibiotics	222 (11·8%)	158 (17·1%)	1785 (12·1%)	0·01	0·14	0·00	0·00
Immunomodulators	260 (13·8%)	106 (11·5%)	3258 (22·0%)	0·21	0·28	0·04	0·01
Dexamethasone	240 (12·8%)	87 (9·4%)	2989 (20·2%)	0·20	0·31	0·04	0·00
Other systemic steroid	18 (1·0%)	22 (2·4%)	244 (1·6%)	0·06	0·05	0·00	0·04
Interferon-beta-1b	10 (0·5%)	4 (0·4%)	195 (1·3%)	0·08	0·10	0·04	0·00
Baricitinib	0	4 (0·4%)	29 (0·2%)	0·06	0·04	0·06	0·02
Tocilizumab	0	0	8 (0·1%)	0·03	0·03	0·03	NA

(Table 1 continues on next page)

	Before 1:1 propensity-score matching					After 1:1 propensity-score matching: standardised mean difference*	
	Molnupiravir recipients (n=1880)	Nirmatrelvir–ritonavir recipients (n=924)	Controls (n=14 810)	Standardised mean difference		Molnupiravir recipients *vs* controls	Nirmatrelvir–ritonavir recipients *vs* controls
				Molnupiravir recipients *vs* controls	Nirmatrelvir–ritonavir recipients *vs* controls		
(Continued from previous page)							
Laboratory parameters at admission							
RT-PCR Ct value							
Mean	22·3 (6·1)	23·2 (7·0)	24·3 (7·4)	0·28	0·15	0·08	0·12
By category	..	..	..	0·36	0·27	0·07	0·05
<20	795 (42·3%)	355 (38·4%)	3904 (26·4%)	..	..	..	..
20 to <30	846 (45·0%)	389 (42·1%)	7753 (52·3%)	..	..	..	..
30 to <35	141 (7·5%)	117 (12·7%)	1846 (12·5%)	..	..	..	..
≥35	98 (5·2%)	63 (6·8%)	1307 (8·8%)	..	..	..	..
Lactate dehydrogenase concentration, U/L	262·0 (193·9)	254·8 (127·8)	278·0 (220·0)	0·07	0·11	0·02	0·00
C-reactive protein concentration, mg/L	46·3 (50·3)	44·2 (49·9)	71·8 (67·6)	0·39	0·41	0·06	0·05
Lymphocyte count, × 10^9 cells per L	1·2 (3·2)	1·2 (2·1)	1·1 (1·3)	0·06	0·05	0·00	0·04

Data are mean (SD) or n (%), unless otherwise indicated. Ct=cycle threshold. NA=not applicable. *Baseline characteristics after propensity-score matching are shown in appendix 2 pp 3–4. †Percentages are based on the number of patients with a symptom onset date reported. ‡Defined as those who had received at least two doses of Comirnaty or three doses of CoronaVac.

Table 1: **Baseline characteristics of molnupiravir recipients, nirmatrelvir–ritonavir recipients, and control groups**

observed between nirmatrelvir–ritonavir recipients (n=783) and matched controls (n=772), whereas length of hospital stay among molnupiravir recipients (n=1667) was slightly shorter than among their matched controls (n=1681; table 2, table 3).

Results of subgroup and sensitivity analyses were largely in line with those of the main analysis (appendix 2 pp 5–12), with some exceptions, including a lack of significant benefit of oral antivirals with regard to all-cause mortality, need for oxygen therapy, or the composite disease progression outcome in patients aged 65 years or younger and in those who had been fully vaccinated.

On day 7 from the index date, the proportion of patients who had died in hospital was lower in molnupiravir recipients (43 [2·3%] of 1856) than in matched controls (98 [5·3%] of 1856) and in nirmatrelvir–ritonavir recipients (12 [1·3%] of 890) than in matched controls (32 [3·6%] of 890), and this difference persisted to day 28 (molnupiravir 140 [7·5%] *vs* controls 276 [14·9%]; nirmatrelvir–ritonavir 31 [3·5%] *vs* controls 83 [9·3%]; figure 3). On day 28, the proportion of patients discharged alive was higher among oral antiviral recipients than among their respective matched controls (molnupiravir 1566 [84·4%] *vs* controls 1398 [75·3%]; nirmatrelvir–ritonavir 797 [89·6%] *vs* controls 734 [82·5%]).

Discussion

In this retrospective cohort of patients with COVID-19 not requiring supplemental oxygen on admission, initiation of molnupiravir or nirmatrelvir–ritonavir was associated with significantly lower risks of all-cause mortality and disease progression, and with reaching a low viral burden faster than their respective matched controls. Oral antiviral use was also associated with a reduced need for oxygen therapy. To our knowledge, this is the first real-world study exploring the inpatient use of oral antivirals during a pandemic wave dominated by the SARS-CoV-2 omicron BA.2 subvariant.

Based on the very limited data on the safety and efficacy of oral antivirals in patients with COVID-19, current guidelines and the medical community are now prioritising their distribution to those who do not require supplemental oxygen but who are at the highest risk of disease progression (ie, who will likely benefit the most from antivirals).[4,11,25,26] Our study cohort reflected such a prescription pattern in real-world clinical practice, and provided real-world evidence supporting their use in those at risk of progression to severe disease—namely, older people with multiple pre-existing comorbidities and who had not been fully vaccinated. The significant risk reduction in disease progression associated with both molnupiravir and nirmatrelvir–ritonavir was mainly

	Molnupiravir recipients (n=1856)			Controls (n=1856)			Molnupiravir recipients *vs* controls	
	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Hazard ratio or mean difference (95% CI)†	p value
All-cause mortality	150 (8·1%)	75 065	19·98 (16·91 to 23·45)	295 (15·9%)	77 495	38·07 (33·85 to 42·67)	0·48 (0·40 to 0·59)	<0·0001
Invasive mechanical ventilation	7 (0·4%)	74 982	0·93 (0·38 to 1·92)	17 (0·9%)	77 343	2·20 (1·28 to 3·52)	0·42 (0·17 to 1·01)	0·052
Intensive care unit admission	1 (0·1%)	75 047	0·13 (0·00 to 0·74)	2 (0·1%)	77 462	0·26 (0·03 to 0·93)	NA	NA
Need for oxygen therapy	192 (11·8%)	60 447	31·76 (27·43 to 36·59)	260 (16·4%)	58 631	44·35 (39·12 to 50·08)	0·69 (0·57 to 0·83)	0·0001
Composite disease progression outcome‡	306 (16·5%)	68 782	44·49 (39·64 to 49·76)	481 (25·9%)	68 846	69·87 (63·76 to 76·40)	0·60 (0·52 to 0·69)	<0·0001
Low viral burden§	274 (17·0%)	18 794	145·79 (129·04 to 164·12)	209 (12·9%)	20 850	100·24 (87·11 to 114·79)	1·38 (1·15 to 1·64)	0·0005
Length of hospital stay, days¶	NA	NA	10·82 (10·41 to 11·23)	NA	NA	11·50 (11·03 to 11·98)	–0·68 (–1·31 to –0·06)	0·033

NA=not applicable. *Crude incidence rates (events per 10 000 person-days) are presented for all outcomes except length of hospital stay, for which the mean is shown. †Hazard ratios are presented for all outcomes with at least two events in each group, except length of hospital stay, for which mean difference is shown; a hazard ratio >1 indicates that molnupiravir recipients had a higher risk of the specified outcome or a shorter time to low viral burden than the matched control group, and vice versa. ‡Includes all-cause mortality, invasive mechanical ventilation, intensive care unit admission, and need for oxygen therapy. §Defined as a cycle threshold value of 30 or higher. ¶Number of participants for this analysis (including only those who were discharged alive) was 1667 for the molnupiravir group and 1681 for the control group.

***Table 2*: Clinical and virological outcomes for molnupiravir recipients compared with matched controls**

	Nirmatrelvir–ritonavir recipients (n=890)			Controls (n=890)			Nirmatrelvir–ritonavir recipients *vs* controls	
	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Hazard ratio or mean difference (95% CI)†	p value
All-cause mortality	32 (3·6%)	31 123	10·28 (7·03 to 14·51)	92 (10·3%)	34 762	26·47 (21·34 to 32·46)	0·34 (0·23 to 0·50)	<0·0001
Invasive mechanical ventilation	6 (0·7%)	31 035	1·93 (0·71 to 4·21)	6 (0·7%)	34 745	1·73 (0·63 to 3·76)	0·97 (0·31 to 3·03)	0·96
Intensive care unit admission	0	31 123	0·00	1 (0·1%)	34 750	0·29 (0·01 to 1·60)	NA	NA
Need for oxygen therapy	79 (10·1%)	25 057	31·53 (24·96 to 39·29)	102 (13·6%)	26 676	38·24 (31·18 to 46·42)	0·73 (0·54 to 0·97)	0·032
Composite disease progression outcome‡	101 (11·3%)	28 827	35·04 (28·54 to 42·57)	173 (19·4%)	31 468	54·98 (47·09 to 63·81)	0·57 (0·45 to 0·72)	<0·0001
Low viral burden§	136 (19·0%)	7269	187·10 (156·97 to 221·31)	105 (14·6%)	8438	124·44 (101·78 to 150·64)	1·38 (1·07 to 1·79)	0·013
Length of hospital stay, days¶	NA	NA	9·59 (9·06 to 10·12)	NA	NA	10·02 (9·35 to 10·69)	–0·43 (–1·29 to 0·42)	0·32

NA=not applicable. *Crude incidence rates (events per 10 000 person-days) are presented for all outcomes except length of hospital stay, for which the mean is shown. †Hazard ratios are presented for all outcomes with at least two events in each group, except length of hospital stay, for which mean difference is shown; a hazard ratio >1 indicates that nirmatrelvir–ritonavir recipients had a higher risk of the specified outcome or a shorter time to low viral burden than the matched control group, and vice versa. ‡Includes all-cause mortality, invasive mechanical ventilation, intensive care unit admission, and need for oxygen therapy. §Defined as a cycle threshold value of 30 or higher. ¶Number of participants for this analysis (including only those who were discharged alive) was 783 for nirmatrelvir–ritonavir group and 772 in the control group.

***Table 3*: Clinical and virological outcomes for nirmatrelvir–ritonavir recipients compared with matched controls**

driven by a substantial reduction in risk of death, which was also illustrated in major clinical trials conducted before the SARS-CoV-2 omicron wave (when the major circulating variant of concern was delta)[27,28] and in some recent studies of nirmatrelvir–ritonavir during an omicron surge.[29,30] Despite the inpatient setting of the current study, our patient population, including those who did not require any supplemental oxygen at baseline, was probably different from that of the MOVe-IN trial, in which the majority of patients presented with moderate-to-severe COVID-19 and approximately half were on oxygen therapy.[31] Additionally, our molnupiravir recipients might not be comparable to those of the MOVe-OUT trial, in which the antiviral was initiated early in non-hospitalised patients with mild-to-moderate COVID-19.[28] A secondary analysis of the MOVe-OUT trial identified a reduced need for respiratory interventions among molnupiravir recipients compared with those treated with placebo, including the patient subgroup who were hospitalised after randomisation.[32] Notably, our results established a significant mortality benefit and reduced disease progression (of increasing oxygen needs) among molnupiravir recipients who were hospitalised and did not require any supplemental oxygen on

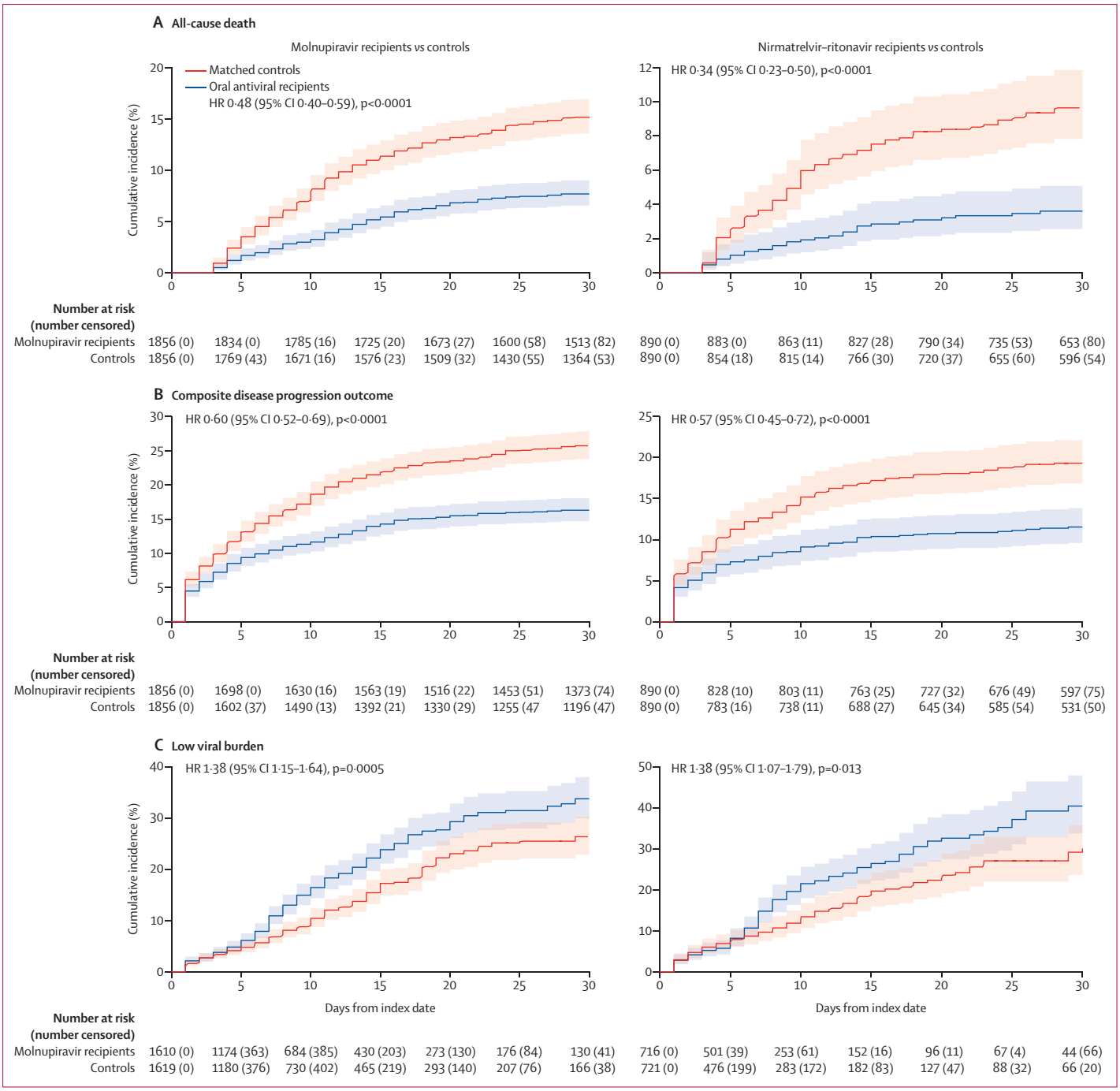

Figure 2: **Cumulative incidence of (A) all-cause mortality, (B) composite disease progression outcome, and (C) low viral burden for molnupiravir recipients and nirmatrelvir–ritonavir recipients versus their respective matched controls**

The composite disease progression outcome consisted of all-cause mortality, initiation of invasive mechanical ventilation, intensive care unit admission, or the need for oxygen therapy. Low viral burden was defined as a cycle threshold of 30 or higher. Shaded regions represent 95% confidence bands. HR=hazard ratio.

admission, whereas these benefits were not evident in the MOVe-IN trial when molnupiravir was initiated at a later and more severe stage of COVID-19.[31]

In terms of viral burden reduction, our patients reached a low viral burden faster with molnupiravir or nirmatrelvir–ritonavir use than with non-use, which adds clinical evidence in support of the efficacy of oral antivirals against the omicron variant of SARS-CoV-2 as shown in experimental studies.[33–38] In studies based on previous variants of concern (including delta), early

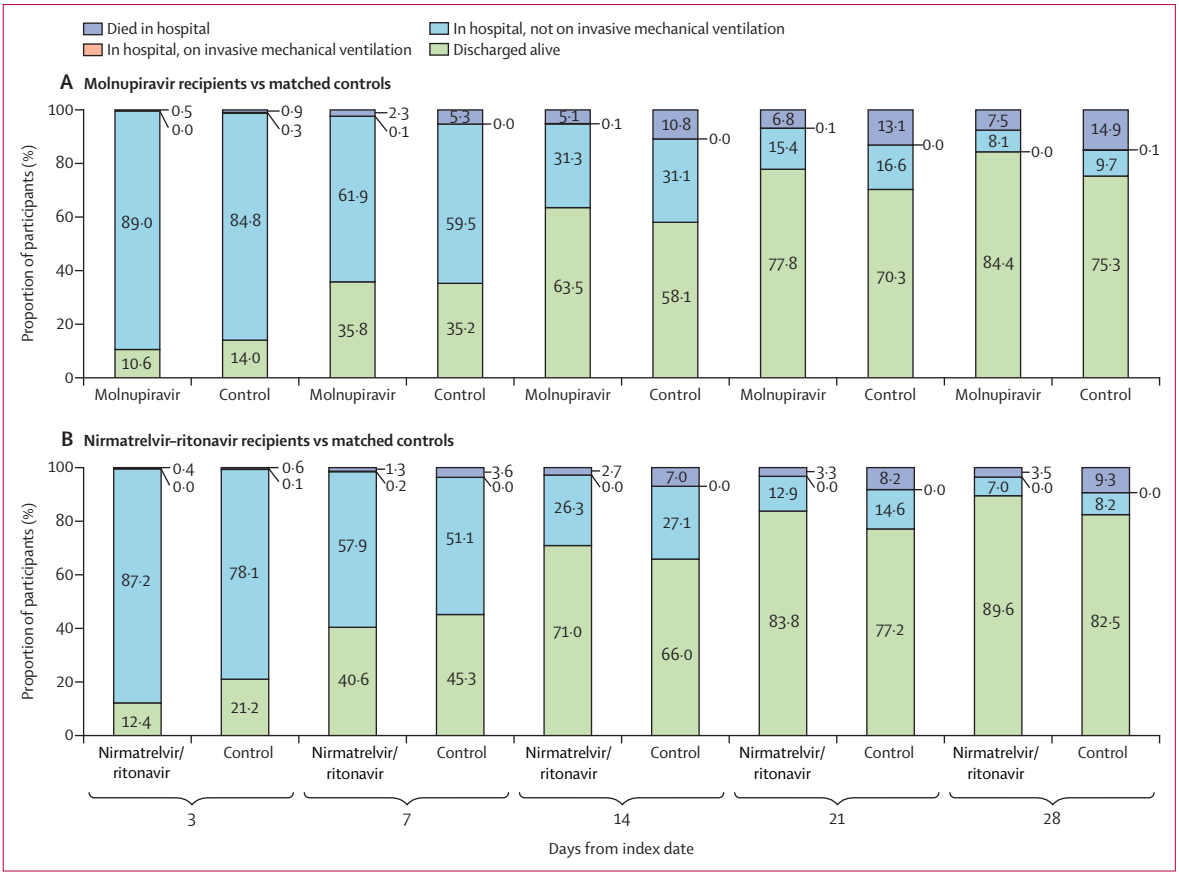

Figure 3: **Comparison of disease status on days 3, 7, 14, 21, and 28 after the index date (hospital admission) between molnupiravir recipients and their matched controls (A), and between nirmatrelvir–ritonavir recipients and their matched controls (B)**

initiation of molnupiravir promoted clinical improvement and symptom resolution in patients with mild-to-moderate COVID-19 and accelerated viral burden reduction, SARS-CoV-2 RNA clearance, and elimination of infectious virus.[28,39–41] The EPIC-HR trial, which was conducted before the omicron variant became prevalent, also showed that nirmatrelvir–ritonavir use was associated with a significant reduction in the viral burden of the delta variant compared with placebo in patients with mild-to-moderate COVID-19.[25,27] To the best of our knowledge, our study is one of the first to offer real-world evidence of oral antiviral use to reduce viral burden in patients with COVID-19 during a pandemic wave of the omicron BA.2 subvariant. This finding is consistent with the faster viral RNA clearance identified with molnupiravir use in the latest clinical trial conducted in hospitalised patients with mild-to-moderate COVID-19 of the omicron variant.[42]

Results of our subgroup analyses suggested a possible lack of significant benefit in younger patients (aged ≤65 years) and those who had been fully vaccinated, which would support prioritising the prescription of oral antivirals to older people and those not adequately vaccinated, who are also likely to be at increased risk of progression to severe COVID-19. Likewise, studies of nirmatrelvir–ritonavir use during a period of high prevalence of the omicron variant have suggested significant clinical and mortality benefits in older people (aged >65 years), yet insufficient evidence for younger patients.[29,30] Nevertheless, further research on the real-world effectiveness of oral antivirals in specific patient populations is needed, as our results could be confounded by the limited sample size, and hence the small number of events, in some patient subgroups.

A strength of the current study is that we used the medical records of patients who were hospitalised and thus closely monitored, and the clinical outcomes and procedures were therefore systematically documented and analysed. Medication adherence could also be guaranteed in an inpatient setting, in contrast to a community setting. Nevertheless, several limitations of our study should be acknowledged. First, we cannot exclude the possibility of selection bias or confounding by indication in this observational study, despite our population-based cohort being fully representative of the local population of patients with COVID-19 not requiring supplemental oxygen on admission. The clinical profile of our patients who were deemed at risk of progression

to severe COVID-19 might differ from those in the major trials of molnupiravir and nirmatrelvir–ritonavir; for instance, the dominant risk factor in those studies was overweight or obesity,[27,28] whereas ours was older age. Moreover, because our study was retrospective, patients who received oral antivirals might have been those considered more in need of treatment than those who remained untreated, despite balanced propensity-score weighting of variables, including those indicating severity. Unfortunately, data on symptom onset date in most patients, and data on oxygen saturation, respiratory rate, and pulse rate (which might have been appropriate indicators of illness severity), were unavailable for this retrospective study. Second, our results could potentially be biased by clinical contraindications related to drug–drug interactions for nirmatrelvir–ritonavir or patient preferences to avoid molnupiravir because of concerns about possible mutagenicity affecting fertility or pregnancy.[43] However, our analysis excluded patients with drug-related contraindications to nirmatrelvir–ritonavir and those with severe renal or liver diseases to allow a fair comparison between oral antiviral recipients and matched controls. Third, because the Ct value was no longer being used as a discharge criterion during our study period, patients might have been deemed clinically stable and discharged before reaching any specific Ct value cutoff. After patients were discharged, follow-up RT-PCR tests were not mandatory, so viral burden of discharged patients could not necessarily be monitored; thus, it is possible that not all patients with COVID-19 would have reached the lower viral burden outcome before hospital discharge (or Ct value was simply not measured before discharge), limiting the interpretation of our results for this outcome. Furthermore, the interpretation of our viral burden results could be dependent on the efficiency of sampling and specimen type and limited by insufficient clinical data on viral infectiousness. Although all hospitals shared the same standard care protocol for patients with COVID-19, including discharge criteria, there was no clear and consistent documentation of the eligibility for discharge for individual patients in the electronic health records. As such, we caution that our length of hospital stay outcome might be specific and not generalisable to other settings. Accordingly, further studies are needed to confirm our findings on viral burden reduction and length of hospital stay associated with oral antiviral use. Finally, the generalisability of our findings could be undermined by the inpatient setting of our cohort, and some of our subgroup analyses were likely to have been underpowered because of their small sample sizes (including the subgroups of younger patients and those who were fully vaccinated). Results from ongoing trials (PANORAMIC,[44] RECOVERY,[45] NCT04746183, and NCT05011513) and observational studies (NCT05195060) are awaited, and further research is needed to explore the safety and effectiveness of oral antivirals in different patient populations (especially by COVID-19 vaccination status and variant of concern), drug combinations, and health-care settings (eg, nursing homes or residential care facilities).

As proposed by the medical and research community, logistics and distribution issues should be adequately addressed by governments and the health-care sector to meet ethical standards and promote optimal and equitable access in the face of limited supplies, such as by developing an evidence-based scoring system or risk prediction tools to help physicians prioritise the distribution of oral antivirals to patients with COVID-19 who would most likely benefit from them.[11,25,26] Notably, some unknown long-term risks associated with molnupiravir use include possible carcinogenicity and teratogenicity, with mutations having been observed in mammalian cells in vitro, and the risk of emergence of more infectious and vaccine-resistant viral variants attributed to the genetic mutations induced.[7–9,46–48] Furthermore, concerns about the development of resistance to molnupiravir and nirmatrelvir–ritonavir have been raised, especially considering the high mutation rates of SARS-CoV-2 and the potential selective pressure induced by extensive use of an antiviral monotherapy.[26,49] Active pharmacovigilance programmes and sequencing of viral mutations are essential to monitoring their long-term safety and effectiveness in different patient populations and waves of the COVID-19 pandemic.[26]

In conclusion, this retrospective cohort study of hospitalised patients with COVID-19 who did not initially require supplemental oxygen showed that early initiation of oral antivirals was associated with significant reductions in risk of all-cause mortality and disease progression, and with reaching a low viral burden faster than non-use, during an epidemic dominated by the SARS-CoV-2 omicron BA.2 subvariant. These findings support the use of these antivirals in this population. As both oral antivirals are currently indicated for non-hospitalised patients with COVID-19 who are at high risk of disease progression, ongoing research will inform the safety and effectiveness of oral antivirals in specific patient populations, drug combinations, and health-care settings.

Contributors

CKHW, GML, and BJC designed the study. The underlying data were verified by CKHW, ICHA, and EHYL. CKHW and ICHA analysed the data. CKHW and KTKL wrote the first draft of the manuscript, which was revised by GML and BJC. All authors interpreted data, provided critical review and revision of the text, and approved the final version of the manuscript. All authors had access to the data underlying the study and accept responsibility for the decision to submit for publication.

Declaration of interests

BJC reports honoraria from AstraZeneca, Fosun Pharma, GlaxoSmithKline, Moderna, Pfizer, Roche, and Sanofi Pasteur. BJC has provided scientific advice to Pfizer and AstraZeneca on issues related to disease burden and vaccine effectiveness; he has not provided scientific advice to either company related to COVID-19 antiviral effectiveness, and he has not received any funding from Pfizer or AstraZeneca for any

research on antiviral effectiveness, including the current work. All other authors declare no competing interests.

Data sharing

The data custodians (the Hospital Authority and the Department of Health of the Government of the Hong Kong Special Administrative Region) provided the underlying individual-patient data to the University of Hong Kong for the purpose of scientific research for the study. Restrictions apply to the availability of these data, which were used under licence for this study. Authors must not transmit or release the data, in whole or in part, and in whatever form or media, or to any other parties or place outside of Hong Kong, and must fully comply with the duties under the law relating to the protection of personal data, including those under the Personal Data (Privacy) Ordinance and its principles in all aspects.

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