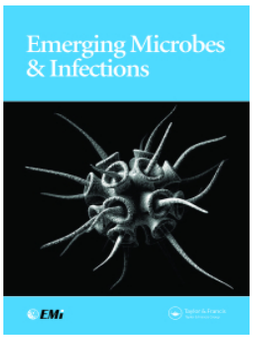

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Effectiveness of nirmatrelvir/ritonavir and molnupiravir on post-COVID-19 outcomes among outpatients: a target trial emulation investigation

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ABSTRACT

Limited studies compared the effectiveness of nirmatrelvir/ritonavir and molnupiravir against a control group on post-COVID-19 conditions. Our study examined the association of nirmatrelvir/ritonavir and molnupiravir with post-acute mortality and hospitalizations among outpatients using real-world outpatient records of COVID-19 designated clinics in Hong Kong. This is an observational study using a target trial emulation framework, involving nirmatrelvir–ritonavir versus no antiviral treatment (Trial 1) and molnupiravir versus no antiviral treatment (Trial 2). Outcomes included post-acute mortality, all-cause hospitalization, and hospitalization due to 13 selected sequelae. Relative effectiveness was assessed by comparing the cumulative incidence between two groups, reported as relative risk (RR), along with risk differences (RD) during day 0–30, 31–180, and 181–360. After screening, 140,477 and 96,030 patients were included in Trial 1 and 2, respectively. Compared with no treatment, nirmatrelvir/ritonavir-treated patients exhibited a significantly lower risk of post-acute mortality (31–180 days: RR, 0.71; 95% CI, 0.54–0.96; RD, 0.20%; 181–360 days: RR, 0.64; 95% CI, 0.50–0.82; RD, 0.32%) and all-cause hospitalization (31–180 days: RR, 0.82; 95% CI, 0.76–0.88; RD, 1.11%; 181–360 days: RR, 0.83; 95% CI, 0.78–0.89; RD, 1.18%). Patients receiving molnupiravir had a lower risk of 30-day mortality, but no significant beneficial effect was observed for the post-acute outcomes. In conclusion, this study demonstrated the effectiveness of nirmatrelvir/ritonavir in reducing post-COVID-19 outcomes among outpatients. While we observed the short-term effectiveness of molnupiravir in reducing mortality, no protective effect on long-term post-COVID-19 outcomes was observed.

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KEYWORDS Post-COVID-19 outcomes; nirmatrelvir/ritonavir; molnupiravir; target trial emulation

ABBREVIATIONS: A&E: accident and emergency; COVID-19: coronavirus disease 2019; HA: hospital authority; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ICPC-2: International Classification of. Primary Care – 2nd Edition; PCC: post-COVID-19 conditions; SMD: standardized mean difference; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; RD: risk difference; RR: relative risk

Background

The continued emergence of new variants of concern of SARS-CoV-2 virus, which exhibit varying levels of severity and transmissibility, remains a key contributor to the mortality and morbidity observed due to coronavirus disease 2019 (COVID-19). The post-COVID-19 conditions (PCC), also known as long COVID or post-COVID sequelae, encompass a spectrum of persistent health consequences experienced by individuals following their initial recovery from COVID-19.

In December 2021, the United States (US) Food and Drug Administration issued emergency use authorization for two pharmacotherapies, namely nirmatrelvir combined with the boosting agent ritonavir (nirmatrelvir/ritonavir) and molnupiravir [1,2]. These medications were authorized for the treatment of symptomatic COVID-19 in non-hospitalized individuals who were at high risks of developing severe COVID-19. The short-term benefits of the antivirals in high-risk patients have been well-documented [3–5], though a recent randomized trial demonstrated that nirmatrelvir/ritonavir did not shorten the time to sustained alleviation of COVID-19 signs and symptoms [6]. Regarding post-COVID-19 conditions,

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studies have yielded inconsistent results on the effectiveness of nirmatrelvir–ritonavir among both non-hospitalized and hospitalized patients [7–10]. While Xie et al. [7] and Wang et al. [8] reported a favourable impact of nirmatrelvir/ritonavir on post-acute mortality and sequelae, Ioannou et al. [9] and Durstenfeld et al. [10] found no association between nirmatrelvir/ritonavir and post-COVID sequelae. Apart from nirmatrelvir/ritonavir, several studies showed that molnupiravir was associated with a lower risk of post-acute conditions [11–14]. For example, Bajema et al. showed that the risk of post-acute death was lower in molnupiravir-treated patients compared to patients without antiviral treatments [11].

While most of the abovementioned investigations have assessed the effectiveness of a single antiviral agent on PCC, only Bajema et al. [11] and Fung et al. [12] compared the effectiveness of nirmatrelvir/ritonavir and molnupiravir against a control group simultaneously in the same investigation. In this study, we used a target trial emulation design to examine the association of nirmatrelvir/ritonavir and molnupiravir with post-acute mortality and hospitalization among outpatients at risk of severe COVID-19 progression in Hong Kong. Our investigation is expected to inform the comparative effectiveness of these two authorized antivirals in an outpatient setting.

Methods

Study design

This is an observational study using a target trial emulation framework, examining the risk of post-acute outcomes following SARS-CoV-2 infection among non-hospitalized adult patients at high risk for progression to severe COVID-19. The target trial involved nirmatrelvir/ritonavir versus no COVID-19 antiviral treatment (Trial 1) and molnupiravir versus no COVID-19 antiviral treatment (Trial 2). The follow-up period was from the date of availability of oral antiviral drugs (i.e. 26 February 2022, for molnupiravir and 16 March 2022, for nirmatrelvir/ritonavir) to 29 January 2023, in Hong Kong. The index date is defined as the date of attendance at COVID-19 designated clinics. The specifications and emulation of the target trial are listed in the Supplementary Table S1.

Data sources

Anonymized clinical data were obtained from the Hong Kong Hospital Authority (HA), which serves over 7.3 million residents and handles more than 90% of all local hospital admissions. The line list of COVID-19 confirmed cases (either by rapid antigen test or polymerase chain reaction test) and vaccination records were obtained from the COVID-19 vaccination registry maintained by the Department of Health. During the Omicron outbreak, HA activated COVID-19 designated clinics to provide outpatient care for confirmed cases with mild symptoms in the community. Health records of the COVID-19 patients were collected, including demographics, death registry information, outpatient records, hospitalization records, accident and emergency (A&E) visits, laboratory results, and medication dispensing records. The diagnoses and procedures were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Primary Care – 2nd Edition (ICPC-2).

Study population and exposure groups

The inclusion criteria were: patients aged 18 years or older who attended COVID-19 designated clinics during the study period, for which Omicron variant was the predominant strain. According to the HA patient management guidelines, patients attending the designated clinics were required to present their positive result of either rapid antigen test or polymerase chain reaction test.

The exclusion criteria were as follows: age under 18 years; having a prior history of COVID-19 before the study period; a prescription record of molnupiravir or nirmatrelvir/ritonavir before the index date; or hospitalization on the index date. For the nirmatrelvir/ritonavir arm, patients with any contraindication to nirmatrelvir/ritonavir within 90 days before the index date were excluded, including history of taking interacting drugs (e.g. amiodarone, lumacaftor–ivacaftor, rifampicin, apalutamide, phenobarbital, rifapentine, carbamazepine, phenytoin, ivosidenib, and primidone), severe liver impairment (e.g. cirrhosis, hepatocellular carcinoma, or liver transplant) or severe renal impairment (e.g. estimated glomerular filtration rate <30 mL/min/1.73 m^2, dialysis, or kidney transplant).

Covariates

Covariates were selected based on previous studies [7,8,11,12,15,16] and were included in the weight model:

1) age
2) sex
3) chronic conditions, including diabetes, chronic lung disease, arrhythmia, hypertension, other cardiovascular diseases, dementia, chronic kidney disease, chronic liver disease, cancer, and human immunodeficiency viral infection. The corresponding ICD-9-CM and ICPC-2 codes can be found in Supplementary Table S2.

4) long-term medications, defined as a prescription issued within 6 months before the index date and lasting for over 90 days. These medications included anti-diabetes, respiratory system drugs, anti-lipid, anti-coagulant and anti-hypertension drugs.
5) concomitant medication initiated at the index date. These medications included any antibiotics, other antiviral drugs, and bronchodilators.
6) vaccination status categorized as fully vaccinated or not fully vaccinated. Fully vaccinated patients received at least three doses of an inactivated vaccine (i.e. CoronaVac by Sinovac®) or at least two doses of an mRNA vaccine (i.e. BNT162b2 by Pfizer-BioNTech®). Doses completed 14 days before the positive PCR date were considered valid.
7) week of the index date
8) month of the study year
9) residential district
10) pre-pandemic public healthcare service utilization, including the numbers of A&E visits, outpatient visits, and hospital admissions during 2018–2019.

Outcomes

The primary outcome is the post-acute in-hospital death, defined as all-cause death occurring 31–180 days and 181–360 days after the index date. The secondary long-term outcomes include all-cause hospitalization and hospitalization due to post-acute sequelae within the same time frames. We selected the 13 post-acute sequelae based on a previous study in the same setting [17]: congestive heart failure, atrial fibrillation, coronary artery disease, deep vein thrombosis, chronic pulmonary disease, acute respiratory distress syndrome, interstitial lung disease, seizure, anxiety, post-traumatic stress disorder, end-stage renal disease, acute kidney injury, and pancreatitis. The corresponding ICD-9-CM codes can be found in Supplementary Table S3. Additionally, short-term outcomes, such as mortality and all-cause hospitalization occurring at the acute phase (i.e. within 30 days after the index date), were also examined.

Statistical analysis

We estimated the intention-to-treat effect of initiating oral antiviral drugs within 5 days of the index date. The date of medication initiation was determined by the prescription record. To adjust for potential selection bias and immortal time bias due to the treatment strategy's 5-day grace period, we employed the cloning-censoring-weighting approach. Each eligible participant was cloned to form synthetic treated and control populations from day zero. Clones violating the assigned treatment strategy were artificially censored (e.g. "treated" clones were censored on day 4 if they had not received an oral antiviral by then, while "control" clones were censored upon initiating antiviral treatment during the grace period). Patients originally assigned to the no-treatment strategy who later received oral antivirals were not censored and remained under the no-treatment strategy. A propensity score for not being censored was generated using logistic regression. This score was used to calculate inverse probability weights stabilized by the proportion of uncensored individuals to balance the covariates (including for age, sex, chronic conditions, long-term medication, concomitant medication prescribed in acute phase of COVID-19, vaccination status, week of index date, study month, residential district, and pre-pandemic public healthcare service utilization) between patients who received the antiviral drugs and those who did not. An illustration of censoring and weighting during the 5-days grace period was showed in Supplementary Table S4. Covariates with an absolute value of standardized mean difference (SMD) $\geq 0{\cdot}1$ after weighting were considered imbalanced.

Cumulative incidence, along with risk differences (RD) between groups, were estimated and reported as percentages during day 0–30, 31–180, and 181–360, respectively. Relative effectiveness was assessed by comparing the cumulative incidence in the treatment arm to the no-treatment arm, reported as relative risk (RR). We further emulated several trials to examine the effect of the antiviral drugs in populations with different characteristics, including vaccination status (not vaccinated vs received at least 1 dose), age (<65 years vs ≥65 years), sex (males vs females), and number of risk factors for progression to severe COVID-19 (≤2 or >2 risk factors). To examine the potential impact of the bias due to susceptibles depletion during the acute phase, a post-hoc analysis was carried to examine the antiviral effect on the outcomes during day 0–180 and 0–360.

Ethics approval and consent to participate

Ethics approval was obtained from the Joint CUHK-NTEC Clinical Research Ethics Committee (Ref No. 2023.006). This study is a retrospective analysis using secondary data without any personal information, so the requirement for obtaining informed consent was waived.

Results

Demographic characteristics of participants

A total of 350,173 and 384,465 patients with COVID-19 were screened in Trial 1 and Trial 2, respectively

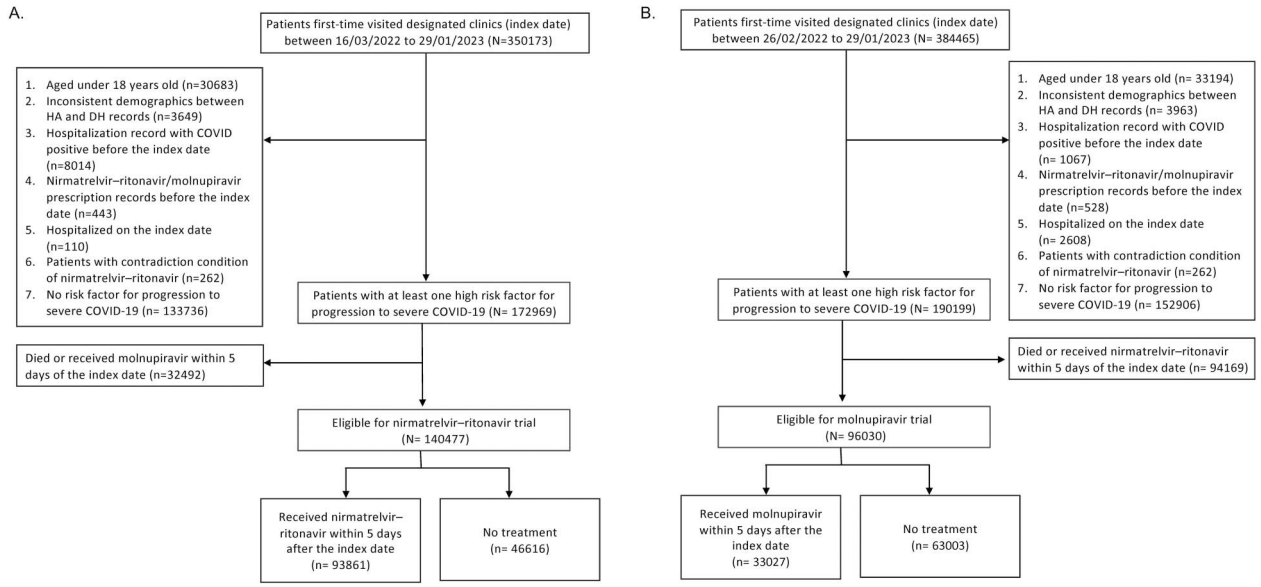

Figure 1. Flowcharts of patient inclusion and exclusion for (A) Trial 1: nirmatrelvir/ritonavir versus no COVID-19 antiviral treatment and (B) Trial 2: molnupiravir versus no COVID-19 antiviral treatment.

(Figure 1). Among the 140,477 patients included in Trial 1, 93,861 received nirmatrelvir/ritonavir and 46,616 received no antiviral treatment; 40,018 (42.6%) and 20,207 (43.4%) were male, with a mean (standard deviation) age of 67.2 (13.1) and 68.6 (15.2) years, respectively (Table 1). Among the 96,030 patients included in Trial 2, 33,027 received molnupiravir and 63,003 received no antiviral treatment; 14,286 (43.3%) and 27,207 (43.2%) were male, with a mean (standard deviation) age of 67.9 (14.5) and 67.8 (15.7) years, respectively. The median (interquartile range) follow-up time for nirmatrelvir/ritonavir and molnupiravir groups were 189 (95–289) and 172 (64–287) days, respectively. No covariates had an absolute value of SMD $\geq$ 0·1 after weighting. The distribution of covariates before weighting is showed in Supplementary Table S5.

Long-term outcomes of nirmatrelvir/ritonavir treatment

Compared with no treatment, nirmatrelvir/ritonavir-treated patients exhibited a significantly lower risk of post-acute outcomes, including lower mortality at 31–180 days (RR, 0.71; 95% CI, 0.54–0.96; p-value, < 0.001) and at 181–360 days (RR, 0.64; 95% CI, 0.50–0.82; p-value, < 0.001) with RD of 0.20% (95% CI, 0.02–0.38) and 0.32% (95% CI, 0.13–0.51), respectively (Figure 2A and Figure 3A). As shown in Figure 2A, a significantly reduced risk in all-cause hospitalization at 31–180 days (RR, 0.82; 95% CI, 0.76–0.88; p-value, < 0.001) and 181–360 days (RR, 0.83; 95% CI, 0.78–0.89; p-value, < 0.001) were observed in nirmatrelvir/ritonavir-treated patients with RD of 1.11% (95% CI, 0.70–1.55) and 1.18% (95% CI, 0.70–1.66), respectively. Lower risks of short-term outcomes during the acute phase were also observed in the nirmatrelvir/ritonavir group.

Among the post-acute sequelae, nirmatrelvir/ritonavir recipients had a lower risk of atrial fibrillation at 31–180 and 181–360 days compared to untreated patients (31–180 days: RR, 0.60; 95% CI, 0.42–0.86; p-value, < 0.001; 181–360 days: RR, 0.61; 95% CI, 0.43–0.88; p-value, < 0.001) (Figure 2A). A similar decreased risk was observed for congestive heart failure and acute kidney injury at 181–360 days in nirmatrelvir/ritonavir-treated patients (RR, 0.62; 95% CI, 0.40–0.95; p-value, < 0.001; RR, 0.57; 95% CI, 0.36–0.96; p-value, < 0.001).

Long-term outcomes of molnupiravir treatment

Compared to the control group, patients receiving molnupiravir had a lower risk of 30-day mortality (RR, 0.59; 95% CI, 0.41–0.92; p-value, < 0.001) with RD of 0.14% (95% CI, 0.02–0.27) (Figure 2B and Figure 3C). However, there was no significant decrease in risk of mortality at 31–180 and 181–360 days in the molnupiravir-treated patients, and their risks of hospitalization at 31–180 and 181–360 days were even higher than the control group. Among the post-acute sequelae, higher risks of end-stage renal disease and seizure were associated with molnupiravir treatment.

Subgroup analysis

Subgroup analyses revealed notable differences in long-term benefits based on vaccination status, age, and the number of risk factors (Supplementary Figures S1–S4). Compared to unvaccinated patients, the effect of nirmatrelvir/ritonavir on mortality at

Table 1. Distribution of covariates in the nirmatrelvir/ritonavir trial and the molnupiravir trial after weighting

	Trial 1			Trial 2		
	No Treatment (n = 46,616)	Nirmatrelvir–ritonavir (n = 93,861)	SMD	No Treatment (n = 63,003)	Molnupiravir (n = 33,027)	SMD
Mean (SD) age (years)	68.57 (15.18)	67.17 (13.11)	−0.10	67.81 (15.74)	67.87 (14.50)	0.00
Sex			−0.01			0.00
Male	20,207 (43.35)	40,018 (42.64)		27,207 (43.18)	14,286 (43.26)	
Female	26,409 (56.65)	53,843 (57.36)		35,796 (56.82)	18,741 (56.74)	
Vaccination status[a]			0.00			0.00
Fully vaccinated	36,148 (77.54)	72,955 (77.73)		46,010 (73.03)	24,149 (73.12)	
Not fully vaccinated	10,468 (22.46)	20,906 (22.27)		16,993 (26.97)	8878 (26.88)	
Vaccine doses						
0 dose	5631 (12.08)	9555 (10.18)	−0.02	9232 (14.65)	3932 (11.91)	−0.03
1 dose	1496 (3.21)	3454 (3.68)	0.00	2553 (4.05)	1977 (5.99)	0.02
2 doses	5407 (11.60)	11,113 (11.84)	0.00	8612 (13.67)	4114 (12.46)	−0.01
≥3 doses	34,081 (73.11)	69,748 (74.31)	−0.02	49,098 (77.93)	25,362 (76.79)	−0.01
Chronic conditions						
Diabetes	8142 (17.47)	15,189 (16.18)	−0.01	10,919 (17.33)	5735 (17.36)	0.00
Chronic lung disease	3704 (7.95)	7127 (7.59)	0.00	5115 (8.12)	2581 (7.81)	0.00
Arrhythmia	859 (1.84)	1989 (2.12)	0.00	1170 (1.86)	546 (1.65)	0.00
Hypertension	17,568 (37.69)	33,763 (35.97)	−0.02	23,573 (37.42)	12,354 (37.41)	0.00
Other CVD	3953 (8.48)	8144 (8.68)	0.00	5420 (8.60)	2652 (8.03)	−0.01
Dementia	1532 (3.29)	3108 (3.31)	0.00	2084 (3.31)	1192 (3.61)	0.00
Chronic kidney disease	1203 (2.58)	2299 (2.45)	0.00	1631 (2.59)	861 (2.61)	0.00
Chronic liver disease	1309 (2.81)	2798 (2.98)	0.00	1774 (2.82)	989 (2.99)	0.00
Cancer	6669 (14.31)	13,681 (14.58)	0.00	9164 (14.54)	4885 (14.79)	0.00
HIV infection	11 (0.02)	28 (0.03)	0.00	18 (0.03)	21 (0.06)	0.00
Long-term medications						
Anti-diabetes	704 (1.51)	1302 (1.39)	0.00	1023 (1.62)	497 (1.51)	0.00
Respiratory drugs	248 (0.53)	518 (0.55)	0.00	358 (0.57)	177 (0.54)	0.00
Anti-lipid	1226 (2.63)	2332 (2.48)	0.00	1744 (2.77)	871 (2.64)	0.00
Anti-coagulant	754 (1.62)	1518 (1.62)	0.00	1114 (1.77)	543 (1.64)	0.00
Anti-hypertension	1495 (3.21)	2913 (3.10)	0.00	2164 (3.43)	1097 (3.32)	0.00
Concomitant medications[b]						
Antibiotics	704 (1.51)	1302 (1.39)	0.00	1023 (1.62)	497 (1.51)	0.00
Other antiviral drugs	157 (0.34)	422 (0.45)	0.00	233 (0.37)	129 (0.39)	0.00
Bronchodilators	813 (1.74)	1689 (1.80)	0.00	1139 (1.81)	665 (2.01)	0.00
Public healthcare service utilization before COVID-19 pandemic						
A&E department visit						
0 times	29,775 (63.87)	60,491 (64.45)	0.01	39,951 (63.41)	20,973 (63.50)	0.00
1–2 times	12,843 (27.55)	25,467 (27.13)	0.00	17,496 (27.77)	9168 (27.76)	0.00
≥3 times	3998 (8.58)	7903 (8.42)	0.00	5556 (8.82)	2886 (8.74)	0.00
Outpatient attendance						
0 times	20,010 (42.92)	40,807 (43.48)	0.01	27,250 (43.25)	13,767 (41.68)	−0.02
1–5 times	9166 (19.66)	18,992 (20.23)	0.01	12,411 (19.70)	6619 (20.04)	0.00
6–10 times	11,802 (25.32)	22,888 (24.38)	−0.01	15,747 (24.99)	8459 (25.61)	0.01
≥10 times	5638 (12.10)	11,175 (11.91)	0.00	7595 (12.05)	4183 (12.66)	0.01
Hospital admission						
0 times	31,671 (67.94)	64,007 (68.19)	0.00	42,703 (67.78)	22,386 (67.78)	0.00
1–2 times	10,772 (23.11)	21,588 (23.00)	0.00	14,552 (23.10)	7593 (22.99)	0.00
≥3 times	4173 (8.95)	8266 (8.81)	0.00	5748 (9.12)	3048 (9.23)	0.00

A&E: Accident and Emergency; CVD: Cardiovascular diseases; HIV: Human immunodeficiency virus; SD: Standard deviation; SMD: Standardized mean difference.

[a]Patients who received at least three doses of an inactivated vaccine (i.e. CoronaVac by Sinovac®) or at least two doses of an mRNA vaccine (i.e. BNT162b2 by Pfizer-BioNTech®) were considered fully vaccinated. Doses completed 14 days before the positive PCR date were considered completed doses.

[b]Concomitant medication initiated at the index date. These medications included any antibiotics, other antiviral drugs and bronchodilators.

31–180 days was more pronounced among those who received at least one dose (RR, 0.91; 95% CI, 0.50–1.69 vs RR, 0.67; 95% CI, 0.50–0.96). Patient aged ≥65 years or having more than two risk factors also had a more pronounced effect of nirmatrelvir/ritonavir on post-acute mortality at 31–180 days. Results of the subgroup analyses in the molnupiravir trial are generally similar to those in the nirmatrelvir/ritonavir trial, but some were inconclusive owing to large uncertainty of the estimates. Compared to the control group, molnupiravir-treated patients aged <65 years had a significant higher risk of acute and post-acute mortalities, and the RRs are apparently higher than that aged ≥65 years (Supplementary Figures S2). The post-hoc analysis of the mortality and hospitalization outcomes at day 0–180 and 0–360 in the nirmatrelvir/ritonavir trial and molnupiravir trial did not show an apparent difference compared to that at day 31–180 and 181–360 (Supplementary Figure S5).

Discussion

In this target trial emulation, we primarily showed that patients treated with nirmatrelvir/ritonavir during the acute phase of SARS-CoV-2 infection had reduced risk of post-acute mortality and hospitalization, compared to those without any antiviral treatment. Among the two similar three-arm studies using US population, only Bajema et al. [11] examined the effectiveness on post-acute mortality, and

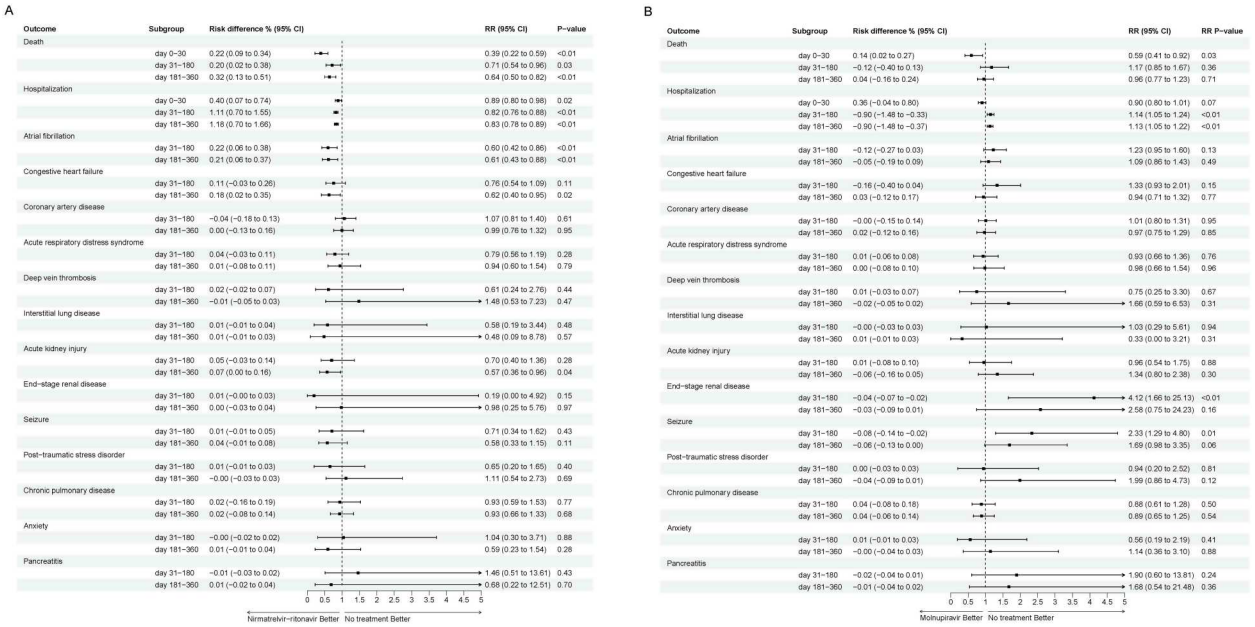

Figure 2. Risk difference and relative risk (RR) of the effect of (A) nirmatrelvir/ritonavir and (B) molnupiravir on study outcomes, compared to no treatment.

our estimated effect size of nirmatrelvir/ritonavir was consistent with their findings, demonstrating a comparable reduction in mortality from 31 to 180 days in non-hospitalized patients (RD: Bajema et al., 0.28% vs. this study, 0.20%). Although they showed an insignificant effect on hospitalization, our study demonstrated a lower risk of post-acute hospitalization, likely due to the larger sample size of our treatment group. Despite differences in the definition of PCC and study population (i.e. elderly), the risk reduction associated with nirmatrelvir/ritonavir in Fung et al. [12] is similar to that observed in our study for post-acute hospitalization.

While our study demonstrated the benefit of molnupiravir in the acute phase, we were unable to show its protective effect on post-acute mortality and hospitalization. Bajema et al. [11] echoed that the benefit of molnupiravir may be more limited compared to nirmatrelvir/ritonavir, though their study still demonstrated a lower risk of post-COVID-19 mortality in molnupiravir recipients compared to untreated participants. Similarly, Xie at al. [14] reported a 39% reduction in the risk of post-acute death with molnupiravir compared to no treatment. We speculate that residual confounding resulting from differential prescription of two antiviral treatments may account for the differences in our findings. According to clinical management guidelines in Hong Kong, both nirmatrelvir/ritonavir and molnupiravir were recommended for patients at risk of progressing to severe COVID-19; however, molnupiravir was rather suggested for those with severe renal and hepatic impairment on top of other risk factors. Consequently, patients with these conditions were likely at higher risk of life-threatening complications after recovering from acute COVID-19, which could explain the increased risk of hospitalization observed with molnupiravir in our study. This explanation was further supported by the observation in our study that the molnupiravir group had higher risk of end-stage renal disease.

Among the 13 post-acute sequelae examined, our study found that atrial fibrillation, congestive heart failure, and acute kidney injury were the sequelae associated with a lower risk in nirmatrelvir/ritonavir-treated patients compared to the untreated patients. Out of 33 PCCs studied by Ioannou et al. [9], they demonstrated that only incidence of thromboembolic events was reduced in the non-hospitalized patients receiving nirmatrelvir/ritonavir. Compared to an investigation including hospitalized patients [8], our study, which focused on at-risk outpatients, found that the effect of nirmatrelvir/ritonavir on reducing post-acute sequelae was less pronounced. This difference may be attributed to the lower prevalence of PCCs in mild cases, suggesting that a larger sample size would likely be required to detect a small effect size in risk reduction of PCCs in our study population [12].

Our subgroup analysis indicated that the effect of nirmatrelvir/ritonavir was more pronounced in vaccinated patients, consistent with several studies that suggest COVID-19 vaccine likely modified effectiveness of antivirals [11,18]. As the immune systems of vaccinated individuals are typically more capable to combat breakthrough infections, the synergistic impact of nirmatrelvir/ritonavir along with the partial immunity conferred by the COVID-19 vaccine may potentially boost the efficacy of nirmatrelvir/ritonavir. Nevertheless, we cannot overlook the potential

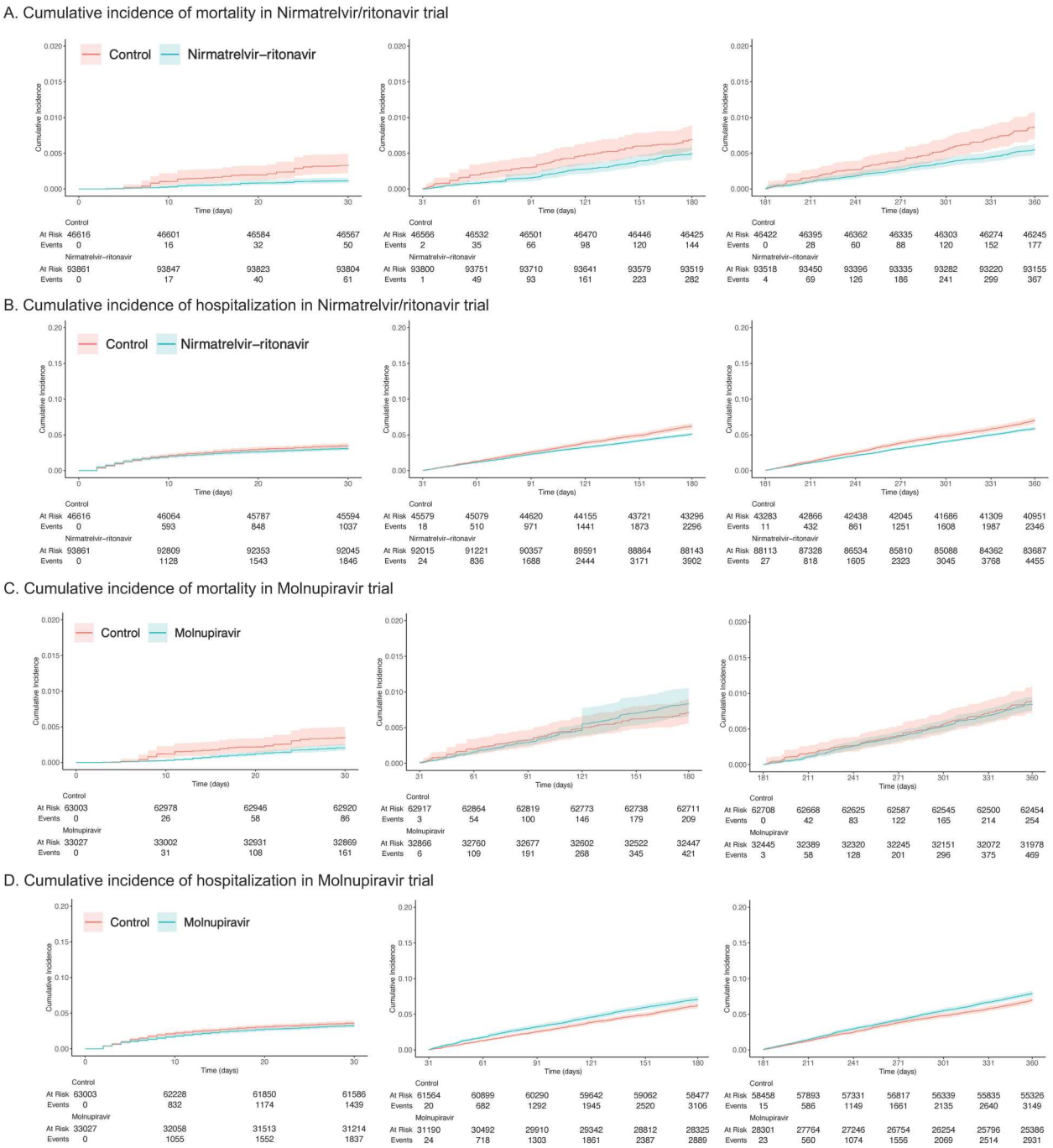

Figure 3. Cumulative incidence curve of study outcomes during 0–30, 31–180, and 181–360 days.

influence of the depletion of susceptibles during the acute phase (i.e. day 0–30), especially considering the greater protective effect observed in the unvaccinated group (resulting in fewer deaths in the post-acute phase). In addition, we showed a more pronounced effect of nirmatrelvir/ritonavir in elderly or those with more than two risk factors of COVID-19 progression. Considering a low prevalence of PCCs in non-hospitalized individuals, the increased vulnerability of these patients to the onset of PCCs may contribute to their greater benefit from antiviral medication [19]. The interpretation of these subgroup analysis findings should be approached with caution, as a limited number of events were observed in certain groups, leading to increased uncertainty (e.g. patients aged <65 years).

Compared with acute outcomes, studies on long COVID-19 often require larger sample sizes and longer follow-up periods, which impedes the implementation of randomized controlled trials. One major strength of this target trial emulation study is its ability to mimic the design and analysis of a hypothetical randomized trial for treatment effect estimation, while also allowing for the use of extensive real-world data. In addition, designated clinics for COVID-19 confirmed cases were specifically launched in Hong Kong during the Omicron outbreak to manage patients with mild symptoms who did not require a hospital

admission. This high coverage of non-hospitalized cases, combined with high-quality clinical and vaccination records, ensures the representativeness of the study samples in a major metropolitan city. Moreover, we restricted the recruitment period so that almost all study patients were infected primarily by sub-lineages BA.2 and BA.5 during the Omicron epidemic in Hong Kong. This minimizes potential variations in the effect sizes of antivirals due to different SARS-CoV-2 variants (e.g. Delta) [20].

Several limitations are noted in this study. Firstly, our study was designed to examine the effectiveness of nirmatrelvir/ritonavir and molnupiravir, excluding other antivirals such as remdesivir due to a relatively small number of outpatient recipients during our study period. Secondly, we assessed a predefined set of 13 sequelae identified through standard ICD codes within the electronic healthcare system [17], rather than the post-COVID-19 conditions defined by the World Health Organization, which mainly include symptom-based outcomes such as fatigue, cognitive dysfunction, and shortness of breath. Nevertheless, both definitions of long COVID-19 are commonly used in literature [14,21]. Thirdly, our study participants in the outpatient clinics had milder illnesses compared to hospitalized patients [8], and thus very few events occurred for several post-acute sequelae, which may introduce sparse data bias. Fourthly, this target trial emulation employed the attendance date at COVID-19 designated clinics as the index date due to a lack of recorded illness onset dates, which may affect the grace period for antiviral prescription. In addition, the ethnicity data was not available in current medical record system; our findings may need validation in populations with different demographic characteristics. However, considering that most patients were symptomatic when attending the designated clinics, and the symptomatic period of an Omicron infection is relatively short [22], we anticipate minimal difference between the illness onset date and attendance date. Lastly, although we have used the target trial framework on the real-world data, unobserved confounders due to unavailability may still result in insufficient confounding adjustment as thus affect the implementation of this trial emulation [23].

Conclusions

In conclusion, our study demonstrated the effectiveness of nirmatrelvir/ritonavir in reducing post-COVID-19 mortality and hospitalization among outpatients at risk of disease progression. While we observed the short-term effectiveness of molnupiravir, we were unable to demonstrate its protective effect on post-COVID-19 outcomes. Our result echoes the clinical guidelines that suggest prescribing nirmatrelvir/ritonavir over molnupiravir if feasible [1,2,24]. The findings of this study thus inform COVID-19 treatment decisions, not only for mitigating disease progression in the acute phase of SARS-CoV-2 infection but also for preventing post-acute conditions.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval and consent to participate

This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline. Ethics approval was obtained from the Joint Chinese University of Hong Kong and New Territories East Cluster clinical research ethics committee, Hong Kong (Ref No. 2023.006). As this study was a retrospective analysis using secondary data without any personal information, the requirement for informed consent was waived.

Contributions

Study design and conceptualization: YWei, CB, KMJ, GL, KCC. Data collection and pre-processing: YWei, HW, CHKY, TYC, ZG, EKY. Data analysis and interpretation: YWei, CB, KMJ, KCC. Writing – Original Draft: YWei, CB, KMJ, HW, GL, CTH, XJ, CL, SZ, CKPM, DSCH, KCC. Writing – Review and Editing: HW, CHKY, TYC, KL, AY, EKY. EKY and KCC have accessed and verified all the data. All authors critically reviewed the manuscript and gave final approval for publication.

Availability of data and materials

The cases' surveillance data and medication records were extracted from electronic records in the system

managed by the Hong Kong Hospital Authority. The vaccine history was extracted from the COVID-19 surveillance database provided by the Department of Health in Hong Kong. Restrictions apply to the availability of these data.

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