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Effectiveness of Molnupiravir and Nirmatrelvir-Ritonavir in CKD Patients With COVID-19

Franco Wing Tak Cheng[1,8], Vincent Ka Chun Yan[1,8], Eric Yuk Fai Wan[1,2,3,8], Celine Sze Ling Chui[2,4,5], Francisco Tsz Tsun Lai[1,2], Carlos King Ho Wong[1,2,3], Xue Li[1,2,6], Irene Ran Zhang[3], Sydney Chi Wai Tang[6], Ian Chi Kei Wong[1,2,7] and Esther Wai Yin Chan[1,2]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [2]Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong Special Administrative Region, China; [3]Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; [4]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; [5]School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; [6]Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; and [7]Aston Pharmacy School, Aston University, Birmingham, UK

Introduction: Even with effective vaccines, patients with CKD have a higher risk of hospitalization and death subsequent to COVID-19 infection than those without CKD. Molnupiravir and nirmatrelvir-ritonavir have been approved for emergency use, but their effectiveness for the CKD population is still unknown. This study was conducted to determine the effectiveness of these drugs in reducing mortality and severe COVID-19 in the CKD population.

Methods: This was a target trial emulation study using electronic health databases in Hong Kong. Patients with CKD aged 18 years or older who were hospitalized with COVID-19 were included. The per-protocol average treatment effect among COVID-19 oral antiviral initiators, including all-cause mortality, intensive care unit (ICU) admission, and ventilatory support within 28 days, were compared to noninitiators.

Results: Antivirals have been found to lower the risk of all-cause mortality, with Molnupiravir at a hazard ratio (HR) of 0.85 (95% confidence interval [CI], 0.77 to 0.95] and nirmatrelvir-ritonavir at an HR of 0.78 [95% CI, 0.60 to 1.00]. However, they do not significantly reduce the risk of ICU admission (molnupiravir: HR, 0.88 [95% CI, 0.59 to 1.30]; nirmatrelvir-ritonavir: HR, 0.86 [95% CI, 0.56 to 1.32]) or ventilatory support (molnupiravir: HR, 1.00 [95% CI, 0.76 to 1.33]; nirmatrelvir-ritonavir: HR, 1.01 [95% CI, 0.74 to 1.37]). There was a greater risk reduction in males and those with higher Charlson Comorbidity Index (CCI). The nirmatrelvir-ritonavir trial also showed reduced risk for those who had antiviral treatment and received 3 or more vaccine doses.

Conclusion: Both molnupiravir and nirmatrelvir-ritonavir reduced mortality rates for hospitalized COVID-19 patients with CKD.

Kidney Int Rep (2024) **9,** 1244–1253; https://doi.org/10.1016/j.ekir.2024.02.009
KEYWORDS: antivirals; CKD; COVID-19; EHR; emulated trial

Individuals with chronic kidney disease (CKD), particularly those with advanced CKD and kidney failure, are at a higher risk for hospitalization and mortality due to COVID-19.[1-3] Although the introduction of effective COVID-19 vaccines has helped to lessen the severity and fatality of COVID-19 in the CKD population,[4] these rates are still significantly higher than those observed in the general population.[5] The attenuated effectiveness could be attributed to diminished antibody responses and the emergence of new variants.[6,7] Therefore, specific treatments for COVID-19 remain to be crucial to reduce the morbidity and mortality rates among this population.

In December 2021, the US Food and Drug Administration granted emergency use authorization for

Correspondence: Esther Wai Yin Chan, Department of Pharmacology and Pharmacy, Room 105G, 1/F, The Jockey Club Building for Interdisciplinary Research (JCBIR), 5 Sassoon Road, Pokfulam, Hong Kong. E-mail: ewchan@hku.hk; or Ian Chi Kei Wong, L2-57, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong. E-mail: wongick@hku.hk

[8]FWTC, VKCY, and EYFW contributed equally to this article.

Received 6 August 2023; revised 9 January 2024; accepted 5 February 2024; published online 9 February 2024

molnupiravir and nirmatrelvir-ritonavir.[8,9] MOVe-OUT and EPIC-HR, both phase 3 randomized clinical trials have demonstrated the efficacy and safety of these 2 antivirals among unvaccinated individuals.[10,11] However, as with other clinical trials for new drugs,[12] patients with advanced CKD and kidney failure were excluded from both trials. Pharmacokinetic studies indicated that kidney impairment has minimal impact on the serum level of molnupiravir;[10] however, it is expected to significantly increase nirmatrelvir-ritonavir exposure in these patients.[13] Further research is therefore warranted to determine the applicability, effectiveness, and safety of these antivirals for the CKD population.

The Hong Kong Department of Health has approved molnupiravir and nirmatrelvir-ritonavir for patients with COVID-19 regardless of vaccination history.[14] Both drugs were made available in February 2022 amid a large local outbreak of COVID-19.[15,16] This study included 2 cohorts of hospitalized patients with COVID-19 who were prescribed either molnupiravir or nirmatrelvir-ritonavir and compared to noninitiators to determine the effectiveness of antivirals in reducing mortality and severe COVID-19 in the CKD population.

METHOD

Data Sources

We collected clinical data from the electronic health record database of the Hospital Authority (HA), vaccination records from the Hong Kong Department of Health, and records of confirmed COVID-19 cases from the Centre for Health Protection of the Government of the Hong Kong Special Administrative Region. We combined these databases using anonymized unique patient identifiers. The HA is a statutory administrative organization in Hong Kong managing all public inpatient services and most public outpatient services. The electronic health record of the HA contains data on patient demographics, diagnoses, prescriptions, and laboratory tests. It provides real-time information to support routine clinical management across all clinics and hospitals in the HA. The Hong Kong Department of Health maintains a database of vaccination records for all individuals in Hong Kong. The Centre for Health Protection maintains a database that documents all confirmed COVID-19 cases based on both mandatory and voluntary reporting of positive results on polymerase chain reaction and rapid antigen tests. These databases, which cover the entire population, have been frequently used in previous studies investigating the risk of adverse effects following COVID-19 vaccinations and other COVID-19 pharmacovigilance studies.[4,17-23]

Study Design and Eligibility Criteria

This is a target trial emulation study using territory-wide observational data in Hong Kong.[24,25] The specification and emulation of the target trial are presented in Supplementary Table S1. Patients with CKD, which is defined either using the International Classification of Diseases, Ninth Revision or eGFR <60 ml/min per 1.73 m^2 measured in the previous 12 months with at least 2 taken ≥ 90 days apart, aged 18 years or older who were hospitalized with COVID-19, defined as a documented COVID-19 infection on the same day as hospital admission, during the inclusion period were recruited. The inclusion period began when COVID-19 oral antiviral drugs became available in Hong Kong (specifically, molnupiravir on February 26, 2022,[15] and nirmatrelvir-ritonavir on March 16, 2022[16]), and ended on July 18, 2022, allowing a 28-day follow-up period before the end of the study of study period (August 15, 2022).

The index date was defined as the date of hospital admission with COVID-19. Exclusion criteria included a history of COVID-19 before the start of the inclusion period; receipt of either molnupiravir or nirmatrelvir-ritonavir before the index date (that is, people who started antiviral treatment in the community setting but required hospitalization due to disease progression); and admission to the ICU, receipt of ventilatory support, or death on the index date. Such patients were excluded due to potential ineligibility for oral medications and possible differences in risk profiles.

For the nirmatrelvir-ritonavir emulated trial, patients with contraindications to nirmatrelvir-ritonavir,[26] including severe liver impairment (cirrhosis, hepatocellular carcinoma, or liver transplant), severe renal impairment (estimated glomerular filtration rate <30 ml/min per 1.73 m^2, dialysis, or kidney transplant), and use of interacting drugs (that is, amiodarone, apalutamide, rifampicin, rifapentine, carbamazepine, primidone, phenobarbital, or phenytoin), within 90 days before the index date were also excluded to minimize residual confounding by indication. Patients were followed-up with from the index date until the earliest occurrence of the specified outcomes, death, or the administrative end of the study (August 15, 2022).

Treatment Strategies

Comparisons of molnupiravir and nirmatrelvir-ritonavir were made using 2 treatment strategies. The first strategy involved initiating either antiviral medication within 5 days of the index date. Separate emulated trials were conducted for each drug. Individuals assigned to this strategy were expected to complete the full 5-day treatment course once it was

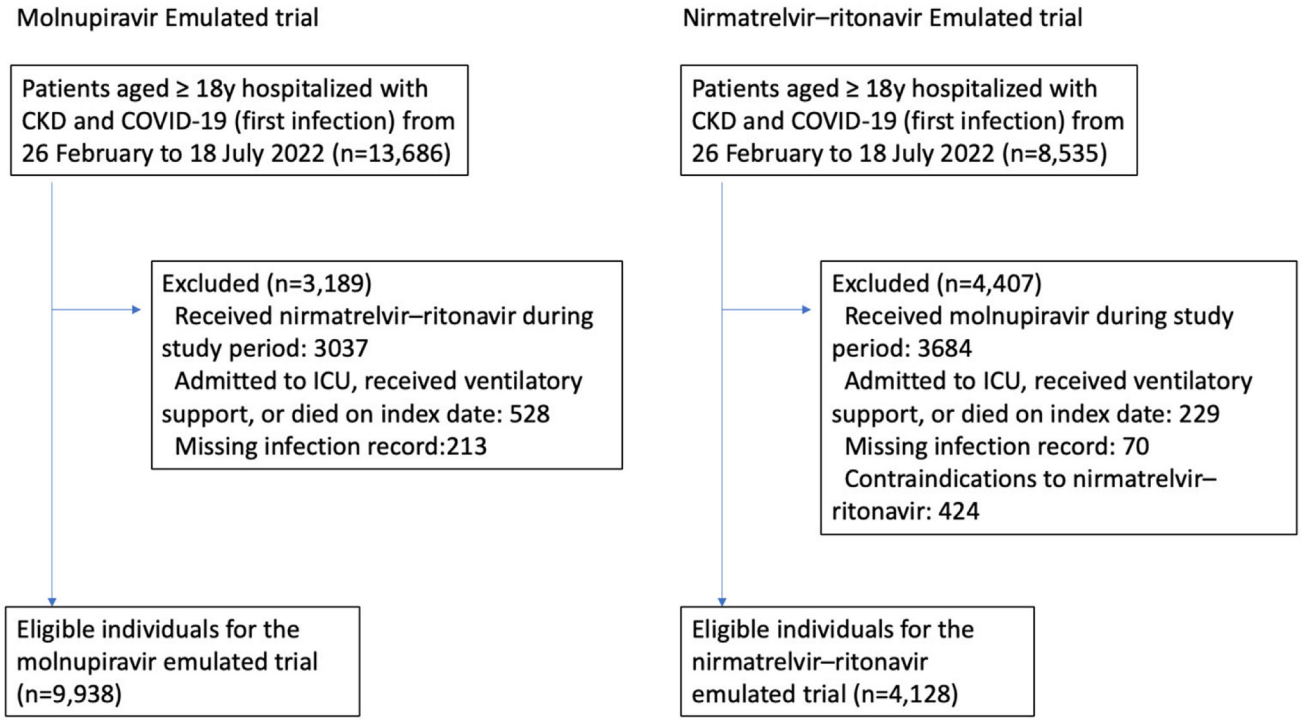

Figure 1. Flowchart of selection. CKD, chronic kidney disease; ICU, intensive care unit.

initiated. Concurrent treatments, such as corticosteroids, were allowed and accounted for as postassignment confounders. The second strategy was no oral antiviral treatment during follow-up.

Outcomes

The primary outcome was all-cause mortality. The secondary outcomes were ICU admission and the use of ventilatory support. Information on all-cause mortality was extracted from the Hong Kong Deaths Registry, an official government registry that documents all registered deaths in Hong Kong. The use of ventilatory support, including intubation, mechanical ventilation, and oxygen supplementation, was identified using procedure codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (39.65, 89.18, 93.90, 93.95, 93.96, 96.04, and 96.7x).

Statistical Analysis

In this emulated target trial, we estimated the per protocol average treatment effect of COVID-19 oral antivirals. To mitigate the potential selection bias and immortal time bias associated with the treatment strategy due to the grace period of 5 days for initiation of COVID-19 oral antivirals, we adopted the cloning, censoring, and weighting approach.[25] Specifically, we created an intermediate data set with 2 copies (clones) of each eligible individual at the index date (day 0) and assigned each clone to one of the treatment strategies. Clones assigned to the "oral antiviral" strategy were artificially censored on day 4 if they had not initiated oral antiviral treatment by then, whereas clones assigned to the "no oral antiviral" strategy were artificially censored upon initiation of oral antiviral treatment during the follow-up period. To account for potential bias introduced with artificial censoring due to baseline and postassignment confounders, stabilized inverse probability weights were estimated, with CCI and concomitant treatments received (remdesivir, tocilizumab, baricitinib, interferon β-1b, or corticosteroids) as postassignment time-varying covariates, in addition to other baseline covariates. The postassignment time-varying covariates were updated daily from the index date until the end of follow-up. Supplementary Table S2 shows the full list of baseline and postassignment covariates included in the pooled logistic regression models that were used in the construction of inverse probability weights.[27,28]

Pooled logistic regression adjusted for treatment, days of follow-up (linear and quadratic term), and baseline covariates (age, sex, CCI, and the number of vaccine doses received) were used to estimate the odds ratio of each outcome, which was used to approximate the HR because the outcomes were considered rare at all times. The 95% CIs were estimated using a robust variance estimator. The selection of these baseline covariates was based on their potential confounding effect on the impact of oral antivirals on mortality. Adjusting for these covariates in the regression model aimed to emulate the randomization of treatment assignment using observational data.

In addition, we estimated the absolute risk differences and the cumulative incidence of outcomes using

Table 1. Baseline characteristics

Characteristics	All eligible individuals	COVID-19 oral antiviral initiators	Noninitiators
Molnupiravir cohort			
Number of individuals	9938	4146	5792
Age, yr, mean (SD)	76.92 (16.09)	77.35 (14.64)	76.61 (17.05)
Sex, male (%)	5452 (54.9)	2236 (53.9)	3216 (55.5)
Charlson Comorbidity Index, mean (SD)	4.79 (2.20)	4.75 (2.07)	4.81 (2.28)
Number of vaccine doses (%)			
Unvaccinated	3255 (32.8)	782 (18.9)	2473 (42.7)
1 dose	1378 (13.9)	332 (8.0)	1046 (18.1)
2 doses	1822 (18.3)	688 (16.6)	1134 (19.6)
≥3 doses	3483 (35.0)	2344 (56.5)	1139 (19.7)
Brand of Vaccine			
Unvaccinated	3255 (32.8)	782 (18.9)	2473 (42.7)
BNT162b2	1438 (14.5)	723 (17.4)	715 (12.3)
CoronaVac	5028 (50.6)	2506 (60.4)	2524 (43.6)
Heterologous	206 (2.1)	126 (3.0)	80 (1.4)
Unknown	11 (0.1)	9 (0.2)	0 (0.0)
eGFR (%)			
<15	981 (12.0)	471 (13.9)	510 (10.7)
15–29	1271 (15.6)	612 (18.0)	659 (13.9)
30–44	2061 (25.3)	886 (26.1)	1175 (24.7)
45–59	3019 (37.1)	1178 (34.7)	1841 (38.8)
≥60	816 (10.0)	251 (7.4)	565 (11.9)
Cancer (%)	968 (9.7)	377 (9.1)	591 (10.2)
Respiratory disease (%)	1010 (10.2)	380 (9.2)	630 (10.9)
Diabetes (%)	4402 (44.3)	1879 (45.3)	2523 (43.6)
Cardiovascular disease (%)	7531 (75.8)	3191 (77.0)	4340 (74.9)
Dementia (%)	503 (5.1)	203 (4.9)	300 (5.2)
Renin-angiotensin-system agents (%)	4922 (49.5)	2157 (52.0)	2765 (47.7)
Beta blockers (%)	3920 (39.4)	1733 (41.8)	2187 (37.8)
Calcium channel blockers (%)	5856 (58.9)	2524 (60.9)	3332 (57.5)
Diuretics (%)	3539 (35.6)	1467 (35.4)	2072 (35.8)
Nitrates (%)	1721 (17.3)	741 (17.9)	980 (16.9)
Lipid lowering agents (%)	5994 (60.3)	2692 (64.9)	3302 (57.0)
Insulins (%)	1925 (19.4)	847 (20.4)	1078 (18.6)
Antidiabetic drugs (%)	3596 (36.2)	1562 (37.7)	2034 (35.1)
Oral anticoagulants (%)	1311 (13.2)	686 (16.5)	625 (10.8)
Antiplatelets (%)	4049 (40.7)	1695 (40.9)	2354 (40.6)
Immunosuppressants (%)	385 (3.9)	203 (4.9)	182 (3.1)
Nirmatrelvir-ritonavir cohort			
Number of individuals	4128	2083	2045
Age, yr, mean (SD)	81.68 (12.34)	82.31 (10.21)	81.03 (14.16)
Sex, male (%)	2256 (54.7)	1142 (54.8)	1114 (54.5)
Charlson Comorbidity Index, mean (SD)	5.04 (1.85)	4.89 (1.65)	5.18 (2.03)
Number of vaccine doses (%)			
Unvaccinated	902 (21.9)	280 (13.4)	622 (30.4)
1 dose	352 (8.5)	71 (3.4)	281 (13.7)
2 doses	798 (19.3)	356 (17.1)	442 (21.6)
≥3 doses	2076 (50.3)	1376 (66.1)	700 (34.2)
Brand of Vaccine			
Unvaccinated	902 (21.9)	280 (13.4)	622 (30.4)
BNT162b2	569 (13.8)	339 (16.3)	230 (11.2)
CoronaVac	2538 (61.5)	1381 (66.3)	1157 (56.6)
Heterologous	113 (2.7)	78 (3.7)	35 (1.7)
Unknown	6 (0.1)	5 (0.2)	1 (0.0)
eGFR (%)			
<15	0 (0.0)	0 (0.0)	0 (0.0)
15–29	0 (0.0)	0 (0.0)	0 (0.0)
30–44	1106 (34.4)	578 (32.5)	528 (36.7)
45–59	2112 (65.6)	1203 (67.5)	909 (63.3)

(Continued on following page)

Table 1. (Continued) Baseline characteristics

Characteristics	All eligible individuals	COVID-19 oral antiviral initiators	Noninitiators
≥60	0 (0.0)	0 (0.0)	0 (0.0)
Cancer (%)	432 (10.5)	214 (10.3)	218 (10.7)
Respiratory disease (%)	446 (10.8)	188 (9.0)	258 (12.6)
Diabetes (%)	1813 (43.9)	902 (43.3)	911 (44.5)
Cardiovascular disease (%)	3206 (77.7)	1603 (77.0)	1603 (78.4)
Dementia (%)	148 (3.6)	51 (2.4)	97 (4.7)
Renin-angiotensin-system agents (%)	2221 (53.8)	1172 (56.3)	1049 (51.3)
Beta blockers (%)	1452 (35.2)	718 (34.5)	734 (35.9)
Calcium channel blockers (%)	2476 (60.0)	1271 (61.0)	1205 (58.9)
Diuretics (%)	1093 (26.5)	387 (18.6)	706 (34.5)
Nitrates (%)	614 (14.9)	271 (13.0)	343 (16.8)
Lipid lowering agents (%)	2646 (64.1)	1370 (65.8)	1276 (62.4)
Insulins (%)	553 (13.4)	222 (10.7)	331 (16.2)
Antidiabetic drugs (%)	1612 (39.1)	836 (40.1)	776 (37.9)
Oral anticoagulants (%)	331 (8.0)	87 (4.2)	244 (11.9)
Antiplatelets (%)	1718 (41.6)	859 (41.2)	859 (42.0)
Immunosuppressants (%)	101 (2.4)	27 (1.3)	74 (3.6)

eGFR, estimated glomerular filtration rate.

predicted values from the pooled logistic regression using the marginal standardization method, with interaction terms between treatment and day of follow-up included. The 95% CIs for the absolute risk difference and cumulative incidence were obtained from a nonparametric bootstrap of 100 samples.

We did prespecified subgroup analyses stratified by vaccination status (0, 1, 2, or ≥3 vaccine doses received), sex (male or female), and CCI (0 to 5 or ≥6). Interaction effects between treatment and vaccination status, age, sex, and CCI (as a continuous variable) were also tested, and the *P*-values for interaction were reported.

All statistical tests were 2-sided, and *P*-values less than 0.05 were considered statistically significant. The statistical analysis was performed using R, version 4.0.3 (R Foundation). To ensure quality assurance, 2 investigators (VKCY and IZ) independently conducted the statistical analyses.

Ethics Approval

This study was approved by the Central Institutional Review Board of the HA of Hong Kong (CIRB-2021-005-4) and the Hong Kong Department of Health Ethics Committee (LM171/2021).

RESULTS

We identified 13,686 and 8535 hospitalized patients with COVID-19 for the emulated trials of molnupiravir and nirmatrelvir-ritonavir, respectively, during their inclusion periods. After exclusion, 9938 eligible participants were included in the molnupiravir trial and 4128 in the nirmatrelvir-ritonavir trial (Figure 1). The mean ages were 76.9 years (SD, 16.1) and 81.7 years (SD, 12.3), respectively, with 54.9% and 54.7% being male sex. In the molnupiravir trial, 1378 (13.9%), 1822 (18.3%), and 3483 (35.0%) participants had received 1, 2, and at least 3 doses of COVID-19 vaccine, respectively. In the nirmatrelvir-ritonavir trial, 352 (8.5%), 798 (19.3%), and 2076 (50.3%) participants had received 1, 2, and at least 3 doses of COVID-19 vaccine, respectively. Other baseline comorbidities are shown in Table 1.

In the emulated trials of molnupiravir and nirmatrelvir-ritonavir, 1567 and 411 participants, respectively, died during follow-up. The HRs of mortality among initiators versus noninitiators were 0.85 (95% CI, 0.77 to 0.95) for molnupiravir and 0.78 (CI, 0.60 to 1.00) for nirmatrelvir-ritonavir (Table 2). The 28-day risks for death in initiators versus noninitiators were 12.94% (95% CI, 11.74% to 13.99%) versus 14.58% (95% CI, 13.71% to 15.71%) (risk difference, −1.64 percentage points [95% CI, −2.78 to −0.56 %-points]) in the molnupiravir trial and 6.70% (95% CI, 5.67% to 7.88%) versus 8.37% (95% CI, 6.89% to 9.92%) (risk difference, −1.67 %-points [95% CI, −3.40 to 0.41 %-points]) in the nirmatrelvir-ritonavir trial (Figure 2 and Supplementary Table S3).

For the outcome of ICU admission, 74 and 10 events occurred during follow-up in the emulated trials of molnupiravir and nirmatrelvir-ritonavir, respectively. The HRs of ICU admission among initiators versus noninitiators were 0.88 (95% CI, 0.59 to 1.30) for molnupiravir and 0.86 (95% CI, 0.56 to 1.32) for nirmatrelvir-ritonavir (Table 2). The 28-day risks for ICU admission in initiators versus noninitiators were 0.68% (95% CI, 0.47% to 0.92%) versus 0.83% (95% CI, 0.59% to 1.02%) (risk difference, −0.15 %-points [95% CI, −0.31 to 0.05 %-points]) in the molnupiravir trial and 0.26% (95% CI, 0.11% to 0.47%) versus

Table 2. Risk for outcomes in COVID-19 oral antiviral initiators compared with noninitiators

	Molnupiravir				Nirmatrelvir-ritonavir			
	No. of events / Follow-up (days)		Adjusted hazard ratio (95% CI)	*P*-value for interaction	No. of events / Follow-up (days)		Adjusted hazard ratio (95% CI)	*P*-value for interaction
Outcome	Initiators	Noninitiators			Initiators	Noninitiators		
All-cause mortality								
Overall	256/108638	1311/137925	0.854 (0.771–0.946)		58/53905	353/51275	0.776 (0.603–0.999)	
Vaccination status								
Unvaccinated	73/20403	781/54501	0.795 (0.695–0.910)		16/7057	141/14900	0.894 (0.634–1.260)	
1 dose	39/8522	231/24903	0.911 (0.715–1.161)	0.45	4/1815	52/6947	0.884 (0.478–1.637)	0.70
2 doses	49/18109	165/28717	0.993 (0.761–1.296)	0.96	18/9221	58/11355	1.002 (0.615–1.632)	1.00
≥3 doses	95/61604	134/29804	0.939 (0.661–1.334)	0.72	20/35812	102/18073	0.430 (0.263–0.705)	< 0.001
Sex								
Male	148/58421	779/75729	0.818 (0.716–0.935)	0.003	36/29599	199/27852	0.723 (0.526–0.993)	0.045
Female	108/50217	532/62196	0.907 (0.776–1.060)		22/24306	154/23423	0.848 (0.599–1.200)	
CCI								
0–5	78/56432	525/76205	0.948 (0.784–1.145)	0.001	27/35045	139/26325	0.813 (0.512–1.290)	0.04
≥6	117/30778	519/37085	0.817 (0.724–0.923)		20/9955	141/15113	0.748 (0.566–0.990)	
ICU Admission								
Overall	20/108236	54/136925	0.875 (0.589–1.300)		2/53889	8/51080	0.859 (0.558–1.322)	
Vaccination status								
Unvaccinated	9/20222	15/54207	1.550 (0.789–3.046)		0/7057	1/14874	1.131 (0.003–456.972)	
1 dose	0/8522	16/24623	0.645 (0.286–1.455)	0.29	0/1815	2/6899	0.769 (0.004–135.880)	0.92
2 doses	3/18056	15/28446	0.591 (0.271–1.287)	0.19	0/9221	2/11308	1.231 (0.016–95.069)	0.93
≥3 doses	8/61436	8/29649	0.808 (0.349–1.873)	0.62	2/35796	3/17999	1.433 (0.041–49.844)	0.84
Sex								
Male	14/58150	34/75119	0.828 (0.514–1.336)	0.44	2/29583	6/27705	1.255 (0.096–16.430)	0.86
Female	6/50086	20/61806	0.974 (0.503–1.884)		0/24306	2/23375	0.994 (0.012–83.702)	
CCI								
0–5	12/56199	29/75609	0.939 (0.569–1.548)	0.44	1/35043	7/26152	1.255 (0.096–16.430)	0.83
≥6	5/30662	12/36887	0.780 (0.417–1.462)		1/9941	0/15113	1.368 (0.084–22.345)	
Ventilation support								
Overall	47/107853	107/136276	1.001 (0.755–1.327)		14/53680	23/50908	1.008 (0.744–1.366)	
Vaccination status								
Unvaccinated	15/20197	42/53861	1.317 (0.857–2.022)		4/6983	5/14826	0.961 (0.333–2.772)	
1 dose	2/8475	23/24558	0.893 (0.443–1.798)	0.75	0/1815	3/6873	1.513 (0.202–11.332)	0.69
2 doses	8/17967	23/28347	0.983 (0.539–1.793)	0.96	2/9208	5/11273	2.894 (0.635–13.188)	0.17
≥3 doses	22/61214	19/29510	0.669 (0.379–1.179)	0.16	8/35674	10/17936	0.496 (0.233–1.058)	0.07
Sex								
Male	33/57865	65/74683	1.085 (0.761–1.548)	0.65	5/29529	12/27639	1.009 (0.412–2.472)	0.98
Female	14/49988	42/61593	0.879 (0.562–1.374)		9/24151	11/23269	0.681 (0.318–1.457)	
CCI								
0–5	17/56091	52/75277	0.914 (0.583–1.432)	0.76	9/34894	11/26099	1.009 (0.412–2.472)	0.26
≥6	19/30490	34/36626	1.057 (0.740–1.510)		2/9910	9/15012	0.689 (0.361–1.315)	

CCI, Charlson Comorbidity Index; CI, Confidence Interval.

0.23% (95% CI, 0.08% to 0.41%) (risk difference, 0.03 %-points [95% CI, −0.08 to 0.15 %-points]) in the nirmatrelvir-ritonavir trial (Figure 2 and Supplementary Table S3).

For the outcome of ventilatory support, 154 and 37 events occurred during follow-up in the emulated trials of molnupiravir and nirmatrelvir-ritonavir, respectively. The HRs of ventilatory support among initiators versus noninitiators were 1.00 (CI, 0.76 to 1.33) for molnupiravir and 1.01 (CI, 0.74 to 1.37) for nirmatrelvir–ritonavir (Table 2). The 28-day risks for ventilatory support in initiators versus noninitiators were 1.65% (CI, 1.32% to 2.00%) versus 1.70% (CI, 1.29% to 2.02%) (risk difference, -0.05 percentage point [CI, −0.34 to 0.33 percentage point]) in the molnupiravir trial and 0.95% (CI, 0.49% to 1.44%) versus 1.29% (CI, 0.64% to 1.99%) (risk difference, −0.34 percentage point [CI, −1.02 to 0.46 percentage point]) in the nirmatrelvir–ritonavir trial (Figure 2 & & Supplementary Table S3).

Significant interactions between oral antiviral treatment and sex and CCI for all-cause mortality were identified. The treatment effects appeared to be more prominent in higher CCI. In the nirmatrelvir-ritonavir trial, it was also observed that there was significant interaction in terms of reducing the risk for those who

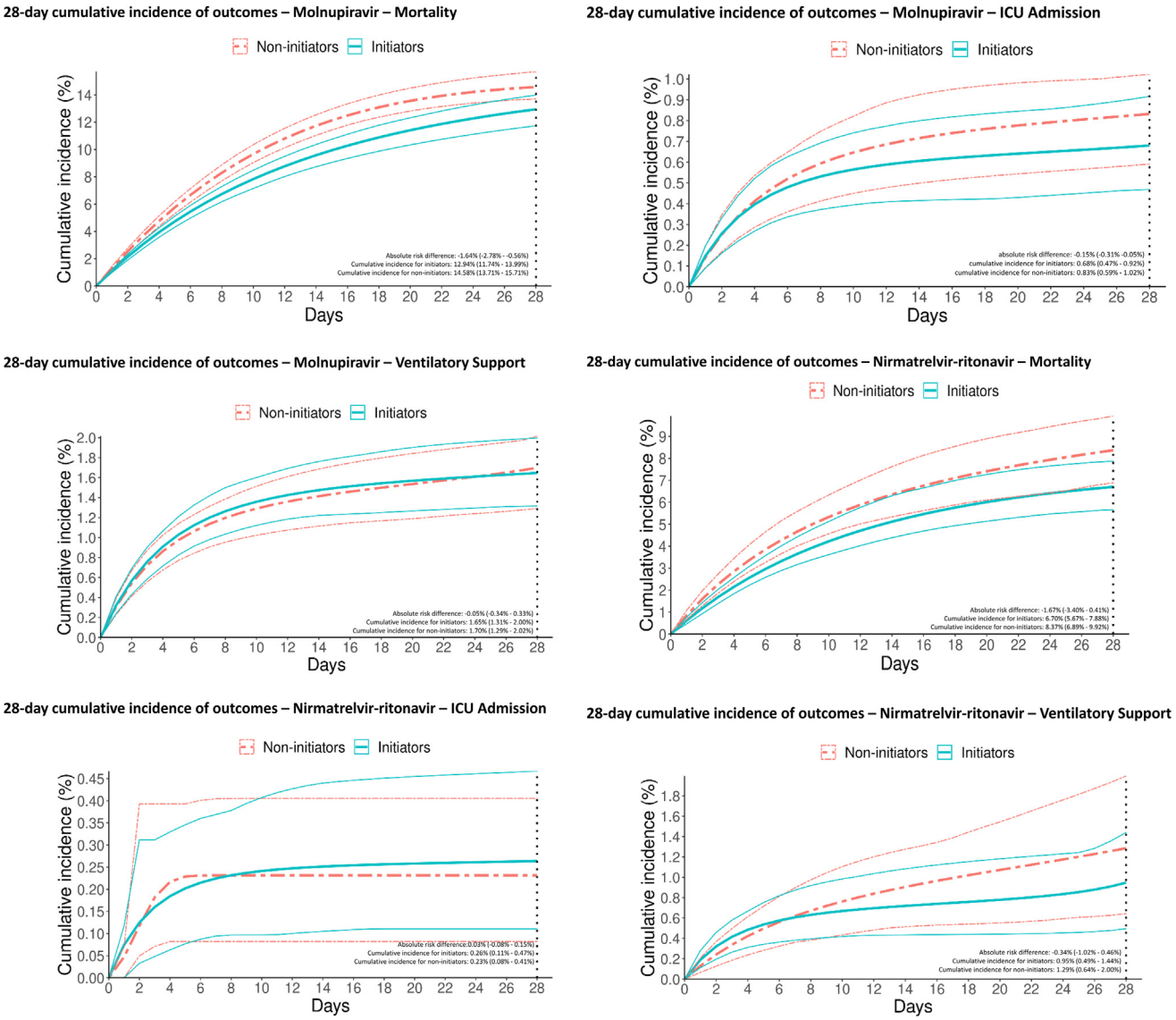

Figure 2. Twenty-eight-day cumulative incidence of outcomes.

received antiviral treatment and had received 3 or more doses of vaccines.

DISCUSSION

To the best of our knowledge, this is the first study to examine the effectiveness of oral antiviral agents for COVID-19 in the CKD population. Our research focused on the effectiveness of molnupiravir and nirmatrelvir-ritonavir in hospitalized COVID-19 patients with CKD during the Omicron-dominant outbreak in Hong Kong. The results showed that both oral antivirals led to a significant decrease in all-cause mortality among patients with CKD compared to the control group, with a magnitude similar to the previous emulated trial conducted in the general population in Hong Kong.

Despite a high risk of progression to severe COVID-19 in the CKD population, there are currently limited data on the safety and efficacy of oral antivirals for this population. In the EPIC-HR trial, only 0.6% of participants had CKD,[11] whereas patients with CKD accounted for just 5.9%, 5.7%, and 1.9% of participants in MOVe-OUT, MOVe-IN, and PANORAMIC studies, respectively.[10,29,30] The lack of representation in clinical trials may have precluded the use of oral antivirals among them. Cho *et al.*[31] reported that only 27 patients with advanced CKD and kidney failure were treated in the first 10 months since the emergency use authorization. Our findings, in conjunction with the ongoing clinical trial (Phase I: NCT05487040), can help fill a critical knowledge gap regarding the effectiveness of oral antivirals in the CKD population.

Our observations suggest that male patients with higher CCI scores are better protected against all-cause mortality when treated with oral antivirals. It has been

noted that, apart from CKD, other underlying conditions such as cardiovascular diseases, cerebrovascular diseases, and diabetes mellitus are associated with severe illness.[32–34] Similarly, studies have shown that males have a disproportionately high number of critical cases and deaths in multiple cohorts worldwide.[34–36] Therefore, the greater protection could, at least partially, be explained by their heightened risk for progression to severe COVID-19 and oral antivirals should be prioritized among these subpopulations.

Although there is no significant interaction between molnupiravir and vaccination status for any outcome, nirmatrelvir-ritonavir appears to be more effective in preventing mortality among those who have received 3 doses or more of COVID-19 vaccines. Contrary to our study, the PANORAMIC study conducted during the Omicron outbreak in the UK did not show lower risks for hospitalization and death with the use of molnupiravir among vaccinated individuals in outpatient settings.[30] It is worth noting that the PANORAMIC cohort had a younger mean age of 56.6 years and only included a small number of patients with CKD. To our knowledge, our study is the first to specifically evaluate a group of molnupiravir-treated patients with CKD. The synergism between antivirals and COVID-19 vaccines reinforces the importance of COVID-19 vaccination for individuals with CKD. Both antivirals and COVID-19 vaccines may have contributed to reducing disease severity and mortality via different mechanisms of action.

We demonstrated the effectiveness of molnupiravir and nirmatrelvir-ritonavir in managing COVID-19 in patients with CKD. Our study used a target trial emulation approach to reduce bias commonly found in observational studies, including immortal time bias and selection bias. Considering that all public hospitals in Hong Kong are managed by the HA, clinical decisions about the initiation of antiviral therapy are guided by recommendations from the HA Central Committee on Infectious Diseases and Emergency Response and thus, clinical practice should be consistent across hospitals. However, our study has limitations, including the lack of a direct comparison between the effectiveness of molnupiravir and nirmatrelvir-ritonavir which warrants further investigation. In addition, underdiagnosis may have occurred as the outcome of ventilator use was solely determined by diagnosis coding in the electronic database, and ICU admission rates were dependent on bed availability. We acknowledge that ICU admission and the need for ventilatory support may not be the most ideal indicators of COVID-19 complications. Further, the timing of symptom onset was not available, and hospital admission with COVID-19 was used as the index date. Finally, there could be unmeasured confounding variables, such as obesity and health behaviors, that may influence vaccine uptake and the risk of COVID-19 complications.

Conclusion

Using population-level data in Hong Kong during the Omicron-dominant outbreak, our study demonstrated that both molnupiravir and nirmatrelvir-ritonavir were associated with a lower risk of death among the hospitalized COVID-19 patients with CKD. However, no significant reduction in ICU admission or the need for ventilatory support was observed.

DISCLOSURE

EYFW has received research grants from the Food and Health Bureau of the Government of the Hong Kong SAR, and the Hong Kong Research Grants Council, outside the submitted work. CKHW reports receipt of General Research Fund, Research Grant Council, Government of Hong Kong SAR; EuroQol Research Foundation, all outside the submitted work. CSLC has received grants from the Food and Health Bureau of the Hong Kong Government, Hong Kong Research Grant Council, Hong Kong Innovation and Technology Commission, Pfizer, IQVIA, and Amgen; personal fees from Primevigilance Ltd.; outside the submitted work. FTTL has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from Food and Health Bureau of the Government of the Hong Kong SAR, outside the submitted work. XL received research grants from Research Fund Secretariat of the Food and Health Bureau (HMRF, HKSAR), Research Grants Council Early Career Scheme (RGC/ECS, HKSAR), Janssen and Pfizer; internal funding from the University of Hong Kong; consultancy fee from Merck Sharp & Dohme, unrelated to this work. EWYC reports grants from Research Grants Council (RGC, Hong Kong), grants from Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, Narcotics Division of the Security Bureau of HKSAR; honorarium from Hospital Authority, outside the submitted work. SCWT reports research funding outside the submitted work from Sanofi, Research Grants Council of Hong Kong, Health and Medical Research Fund of Hong Kong, and National Natural Science Foundation of China, and also received speaker fees from AstraZeneca, Novartis, and Bayer in the previous 3 years. He is also on the Executive Committee of Kidney Diseases: Improving Global Outcomes, Steering Committee of Eledon Pharmaceuticals, and provides scientific advice to Travere Therapeutics. ICKW reports research

funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong RGC, and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, and also received speaker fees from Janssen and Medice in the previous 3 years. He is also an independent nonexecutive director of Jacobson Medical in Hong Kong. All the other authors declared no conflicting interests.

ACKNOWLEDGMENTS

We gratefully acknowledge the Centre for Health Protection, Department of Health, and Hospital Authority for facilitating data access.

FUNDING

This work was supported by a research grant from the Food and Health Bureau; HMRF Research on COVID-19, The Government of the Hong Kong Special Administrative Region (Principal Investigator (WP2): EWC; Ref: COVID1903011). ICKW and FTTL are partially supported by the Laboratory of Data Discovery for Health (D24H) funded by AIR@InnoHK administered by Innovation and Technology Commission.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE statement.

Table S1. Target trial specification and emulation using observational data.

Table S2. Baseline and postassignment covariates for the construction of inverse probability weights.

Table S3. Survival probability for outcomes in COVID-19 oral antiviral initiators compared with noninitiators.

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