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Comparing the effectiveness of molnupiravir and nirmatrelvir-ritonavir in non-hospitalized and hospitalized COVID-19 patients with type 2 diabetes: A target trial emulation study

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Abstract

Aims: To compare the effectiveness of molnupiravir and nirmatrelvir-ritonavir for non-hospitalized and hospitalized COVID-19 patients with type 2 diabetes (T2DM).

Materials and Methods: Territory-wide electronic health records in Hong Kong were used to perform target trial emulation using a sequential trial approach. Patients (1) aged ≥18 years, (2) with T2DM, (3) with COVID-19 infection, and (4) who received molnupiravir or nirmatrelvir-ritonavir within 5 days of infection between 16 March 2022 and 31 December 2022 in non-hospital and hospital settings were included. Molnupiravir and nirmatrelvir-ritonavir initiators were matched using one-to-one propensity-score matching and followed for 28 days. Risk of outcomes was compared between groups by Cox regression adjusted for baseline characteristics. Subgroup analyses were performed on age (<70 years, ≥70 years), sex, Charlson comorbidity index (<4, ≥4), and number of COVID-19 vaccine doses (<2 doses, ≥2 doses).

Eric Y.F. Wan and Zoey C.T. Wong are co-first authors with equal contributions.

Results: Totals of 17 974 non-hospitalized (8987 in each group) and 3678 hospitalized (1839 in each group) patients were identified. Non-hospitalized nirmatrelvir-ritonavir initiators had lower risk of all-cause mortality (absolute risk reduction [ARR] at 28 days 0.80%, 95% confidence interval [CI] 0.56–1.04; hazard ratio [HR] 0.47, 95% CI 0.30–0.73) and hospitalization (ARR at 28 days 4.01%, 95% CI 3.19–4.83; HR 0.73, 95% CI 0.66–0.82) as compared with molnupiravir initiators. Hospitalized nirmatrelvir-ritonavir initiators had reduced risk of all-cause mortality (ARR at 28 days 2.94%, 95% CI 1.65–4.23; HR 0.56, 95% CI 0.40–0.80) as compared with molnupiravir initiators. Consistent findings were found across all subgroups.

Conclusions: The use of nirmatrelvir-ritonavir may be preferred to molnupiravir for COVID-19 patients with T2DM and without contraindication to either treatment.

KEYWORDS

effectiveness, pharmacoepidemiology, real-world evidence, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus (DM) affected approximately 463 million people worldwide in 2019, which accounts for a global prevalence of approximately 9.3%.[1] Since 2020, the global outbreak of COVID-19 has led to over 767 million confirmed cases, of which 6.94 million resulted in death.[2] During the COVID-19 pandemic, DM was reported as a comorbidity among COVID-19 patients.[3] However, studies have shown a significant association of pre-existing DM with increased risk of all-cause mortality, hospitalization and severe COVID-19 among COVID-19 patients versus those without DM.[4–8] COVID-19 infection was also found to be associated with increased risk of DM development as compared with a control group (without COVID-19 infection or with influenza infection).[9,10] Hyperglycaemia may activate angiotensin-converting enzyme 2, the receptor of SARS-CoV-2, promoting entry of the virus into cells.[11] High blood glucose levels may also affect innate and adaptive immunity, and alter inflammatory response.[12,13] Despite the availability and efficacy of vaccination against COVID-19, patients with DM may have a lower antibody response towards vaccines.[14] Therefore, effective antiviral agents are urgently needed for treating COVID-19 patients with DM.

Molnupiravir (Lagevrio) and nirmatrelvir-ritonavir (Paxlovid) are two antiviral drugs that have been demonstrated to be effective oral treatments for COVID-19. However, direct comparison between the efficacy of these two antiviral agents in COVID-19 patients with DM remains scarce. In two Phase III randomized controlled trials, the Molnupiravir for Oral Treatment of COVID-19 in an Outpatient Setting (MOVe-OUT) trial and the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial, molnupiravir and nirmatrelvir-ritonavir reduced the relative risk of hospitalization or mortality by 31% and 89%, respectively, as compared with placebo.[15,16] The result was consistent in the subgroup of patients with DM in the EPIC-HR trial, which evaluated the efficacy of nirmatrelvir–ritonavir.[16] In the MOVe-OUT study, however, molnupiravir did not reduce the risk of hospitalization and mortality in patients with DM as compared with placebo.[15] In another randomized controlled trial, PANORAMIC, for COVID-19 patients with or without DM, the difference in hospitalization or death between the group receiving molnupiravir and that receiving usual care was insignificant.[17] In two observational studies, significant risk reduction for all-cause mortality and hospitalization among non-hospitalized COVID-19 patients with DM was reported for both molnupiravir and nirmatrelvir-ritonavir.[18,19] However, since the study design and patient populations varied across studies, indirect comparison of the effectiveness of molnupiravir versus nirmatrelvir-ritonavir may not be appropriate. Currently, due to the efficacy of nirmatrelvir-ritonavir and insignificant impact from molnupiravir in reducing the risk of hospitalization or mortality demonstrated in the EPIC-HR and PANORAMIC trials, respectively, the use of nirmatrelvir-ritonavir is recommended over molnupiravir among patients with no contraindications to either drug. These include the clinical guidelines from the National Institutes of Health in the United States and the National Health and Medical Research Council in Australia.[20,21] In Hong Kong, as proposed by the Hospital Authority (HA), the use of nirmatrelvir-ritonavir is also recommended over molnupiravir for patients with early onset of disease and at risk of progression to severe COVID-19.[22] Given the priority given to nirmatrelvir-ritonavir over molnupiravir in existing guidelines and the potential link between COVID-19 and DM, evidence of the comparative effectiveness of these two treatments among this specific population is crucial.

Head-to-head direct comparison of the efficacy of molnupiravir and nirmatrelvir-ritonavir among patients with type 2 diabetes (T2DM) is limited. In Hong Kong, the use of both antiviral agents has been approved by the Department of Health.[23,24] The drugs have been distributed to COVID-19 patients aged over 60 years or at high risk of medical illness, in both non-hospital and hospital settings. However, there is no specification for patients with T2DM as a comorbidity.[25] Therefore, using a target trial emulation design, we aimed to compare the effectiveness of molnupiravir and nirmatrelvir-ritonavir

in both non-hospitalized and hospitalized COVID-19 patients with T2DM based on a large real-world population.

2 | METHODS

2.1 | Data sources

Clinical data were retrieved from the HA's routine electronic health records database, records of vaccination and confirmed COVID-19 case were retrieved from the Department of Health of the Government of the Hong Kong Special Administrative Region (HKSAR), and death records were extracted from the Hong Kong Deaths Registry. In Hong Kong, all public inpatient and most public outpatient services are managed by the HA. The electronic health records database from the HA contains demographics, diagnoses, prescriptions, and laboratory tests for each patient, which support clinical management in all clinics and hospitals within the HA. The Department of Health maintains the database of vaccination records for all individuals in Hong Kong, as well as confirmed COVID-19 cases, based on both mandatory and voluntary reporting of positive polymerase chain reaction (PCR) and rapid antigen test results. The Hong Kong Deaths Registry is a government agency under the HKSAR government, which maintains records of registered deaths for all Hong Kong residents. These databases have been frequently used in studies to evaluate the effectiveness of COVID-19 drugs and vaccinations at population level.[26–29] Patients with T2DM were identified by International Classification of Primary Care, Second Edition (ICPC-2) code T90 or International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 250.x0 or 250.x2, with exclusion of patients with type 1 diabetes (ICPC-2 code T89 or ICD-9-CM code 250.x0 or 250.x2).

2.2 | Study design and eligibility criteria

In this study, target trial emulation was adopted using territory-wide electronic health records databases in Hong Kong. Target trial emulation was used to attenuate some common biases in observational studies such as immortal time and selection biases.[30–32] Details of the specification and emulation of the trial are provided in Supplementary Table S1. Subjects in Hong Kong who (1) were aged ≥18 years, (2) had pre-existing T2DM, (3) had COVID-19 infection and (4) received COVID-19 oral antiviral agents (molnupiravir or nirmatrelvir-ritonavir) within 5 days of infection between 16 March 2022 (when both molnupiravir and nirmatrelvir-ritonavir became available in Hong Kong) and 31 December 2022 were included. The index date was defined as the first date of molnupiravir or nirmatrelvir-ritonavir prescription. Patients who (1) had a history of COVID-19 infection or (2) had contraindications to nirmatrelvir–ritonavir or molnupiravir were excluded. The contraindications included severe liver impairment (cirrhosis, hepatocellular carcinoma, or liver transplant), chronic kidney disease, and use of interacting drugs (amiodarone, apalutamide, rifampicin, rifapentine, carbamazepine, primidone, phenobarbital, phenytoin, or direct oral anticoagulants) within 90 days before index date.[33,34] Patients who had a history of each outcome before the index date were excluded from analysis.

2.3 | Sequential trial emulation

Two emulated target trials were conducted in a sequential trial approach separately for non-hospitalized and hospitalized patients, respectively.[35,36] Non-hospitalized patients were defined as patients who were not hospitalized on or before index date, and hospitalized patients referred to those admitted to hospital on or within 5 days before index date. One-to-one propensity-score matching was performed between eligible molnupiravir and nirmatrelvir-ritonavir initiators identified each week during the inclusion period. Hence, matching was performed for each of the 84 trials (42 trials in each group). The calliper was set at 0.2 to emulate randomization of treatment assignment, and the propensity scores of each subject were estimated with logistic regression. The probability of each treatment was predicted by baseline covariates that were potential confounders of COVID-19 oral antiviral agents and death, including age, sex, Charlson comorbidity index (CCI), number of doses of COVID-19 vaccination, duration of T2DM, pre-existing comorbidities (cancer, respiratory disease, hypertension, DM-related complications [cardiovascular disease, peripheral vascular disease, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy]), and use of medication (renin-angiotensin-system agents, beta blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulin, sulphonylureas, metformin, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose cotransporter-2 [SGLT2] inhibitors and glucagon-like peptide-1 [GLP-1] agonists) within 90 days before index date. The matched patients were combined as a single cohort. Each subject was followed up from the index date till the earliest outcome occurrence, all-cause mortality, 28 days from index date or the end of data availability (31 January 2023).

2.4 | Outcomes

The outcomes for evaluation of effectiveness included (1) 28-day all-cause mortality, (2) intensive care unit (ICU) admission or ventilatory support within 28 days, and (3) hospitalization within 28 days (for community settings only). Ventilatory support was identified using ICD-9 procedure codes (39.65, 89.18, 93.90, 93.95, 93.96, 96.7, and 96.04).

2.5 | Statistical analysis

The balance of baseline covariates between matched cohorts was assessed using standardized mean difference (SMD). An SMD ≤0.1 for all covariates was considered acceptable.[37] Incidence rates were reported and corresponding 95% confidence intervals (CIs) were

estimated by Poisson distribution. Comparison of the risk of outcomes in molnupiravir versus nirmatrelvir-ritonavir initiators was performed by Cox proportional hazards regression on the matched dataset adjusted for baseline covariates used in estimation of propensity score, in which hazard ratios (HRs) with 95% CIs were reported. Proportional hazard assumption was checked by testing for independence between scaled Schoenfeld residuals with time. Global tests for the models were performed, which resulted in insignificant p values of 0.087 (non-hospitalized group) and 0.662 (hospitalized group). Hence, the assumption was satisfied. Absolute risk reduction (ARR) was reported as the difference in rate of events between patients who received nirmatrelvir-ritonavir and patients who received molnupiravir.

Subgroup analyses stratified by age (<70 years, ≥70 years), sex (male, female), CCI (<4, ≥4), and COVID-19 vaccination status (<2 doses, ≥2 doses) were performed. Interaction effects between treatment and age (continuous variable), sex, CCI (continuous variable), and vaccination status were also tested, with p values of interaction reported. In addition, seven sensitivity analyses were performed to evaluate the robustness of the findings from the main analysis. Inverse probability weighting was applied on Cox proportional hazards regression without application of one-to-one propensity-score matching. Patients with baseline history of (1) diabetic neuropathy, (2) use of diuretics within 90 days, (3) use of insulin within 90 days, (4) use of dipeptidyl peptidase-4 (DPP-4) inhibitors within 90 days and (5) diabetic neuropathy, or use of diuretics, insulin or DPP-4 inhibitors within 90 days were excluded in each of the five sensitivity analyses due to slight imbalance between groups among hospitalized patients (SMD >0.1). E-value was also computed to assess the robustness of conclusions to potential unmeasured confounding.[38]

All statistical tests were performed using R version 4.0.3 (www.R-project.org). All tests of significance were two-tailed, with p values ≤0.05 taken to indicate statistical significance.

For quality assurance purposes, two researchers (Z.W., V.Y.) carried out the statistical analyses independently. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist was applied to ensure transparent reporting of this cohort study.

2.6 | Ethics committee approval

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

2.7 | Role of the funding source

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

3 | RESULTS

Totals of 17 974 non-hospitalized (nirmatrelvir-ritonavir 8987; molnupiravir 8987) and 3678 hospitalized (nirmatrelvir-ritonavir 1839; molnupiravir 1839) patients were included after the application of one-to-one propensity-score matching to eligible subjects (Figure 1). The baseline characteristics of patients are shown in Table 1. The distribution of index dates for eligible patients after matching is shown in Supplementary Figure S1. For non-hospitalized patients, the mean (SD) age of nirmatrelvir-ritonavir initiators was 72.87 (10.32) years, with 49.2% male patients, and the mean (SD) age of molnupiravir initiators was 73.82 (11.38) years, with 49.1% male patients. In both treatment groups, the majority of patients were vaccinated with either BNT161b2 or CoronaVac (≥3 doses: nirmatrelvir-ritonavir 77.5% vs. molnupiravir 75.6%; ≥2 doses: nirmatrelvir-ritonavir 90.5% vs. molnupiravir 88.3%). All baseline characteristics were well balanced between the two treatment groups, with an SMD ≤0.1, except for CCI (SMD 0.107; Table 1). For hospitalized patients, the mean (SD) age of nirmatrelvir-ritonavir initiators was 77.80 (10.75) years, with 49.3% male patients, and the mean (SD) age of molnupiravir initiators was 77.97 (11.66) years, with 49.7% male patients. Similarly to non-hospitalized patients, most patients from both treatment groups were vaccinated (≥3 doses: nirmatrelvir-ritonavir 65.0% vs. molnupiravir 62.8%; ≥2 doses: nirmatrelvir-ritonavir 82.4% vs. molnupiravir 79.7%). All baseline characteristics were well balanced between the two treatment groups with SMD ≤0.1, except for CCI (SMD 0.149), pre-existing diabetic neuropathy (SMD 0.147), use of diuretics (SMD 0.123), insulin (SMD 0.152) and DPP-4 inhibitors (SMD 0.140; Table 1). The baseline characteristics of eligible patients before matching are also shown in Supplementary Table S2.

The 28-day cumulative incidence of outcomes in the two groups is shown in Figure 2. For non-hospitalized patients, as compared with molnupiravir initiators, nirmatrelvir-ritonavir initiators had lower rates of all-cause mortality (ARR at 28 days 0.80%, 95% CI 0.56–1.04) and hospitalization (ARR at 28 days 4.01%, 95% CI 3.19–4.83), and a similar rate of ICU admission or ventilatory support (ARR at 28 days 0.07%, 95% CI −0.09 to 0.22; Table 2). For hospitalized patients, similarly, the rate of all-cause mortality was lower in nirmatrelvir-ritonavir than molnupiravir initiators (ARR at 28 days 2.94%, 95% CI 1.65–4.23), and the rate of ICU admission or ventilatory support was similar in the two treatment groups (ARR at 28 days: −0.22%, 95% CI −0.67 to 0.23; Table 2). The result was consistent with adjusted relative risk, in which nirmatrelvir-ritonavir was significantly associated with reduced risk of all-cause mortality (HR 0.47, 95% CI 0.30–0.73) and hospitalization (HR 0.73, 95% CI 0.66–0.82) among non-hospitalized patients, and with reduced risk of all-cause mortality in hospitalized patients (HR 0.56, 95% CI 0.40–0.80; Table 2).

Similar results were found in all-cause mortality among both non-hospitalized and hospitalized individuals across all subgroups (Table 3). The findings on ICU admission or ventilatory support and hospitalization were also consistent across all subgroups for both non-hospitalized and hospitalized patients (Supplementary Table S3). The results from six sensitivity analyses were similar to those of the

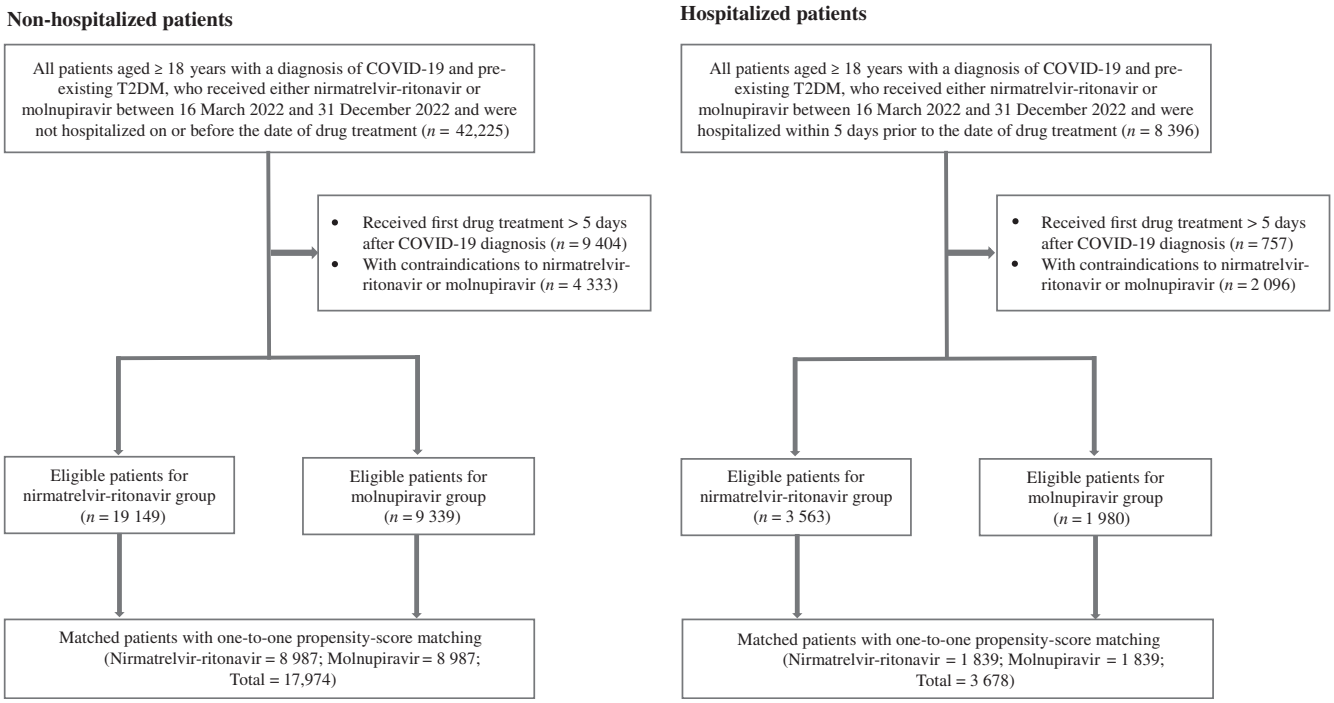

FIGURE 1 Study flow diagram. Patients were matched by gender, age, Charlson Comorbidity Index, vaccination status, pre-existing comorbidities and medication use within 90 days at baseline. T2DM, type 2 diabetes.

main analysis, including the application of inverse probability weighting without one-to-one propensity-score matching and the exclusion of patients with (1) pre-existing cardiovascular disease, (2) use of diuretics within 90 days, (3) use of insulin within 90 days, (4) use of DPP-4 inhibitors within 90 days, and (5) pre-existing cardiovascular disease, or use of diuretics, insulin or DPP-4 inhibitors within 90 days. (Supplementary Table S4–S8). The E-values for all-cause mortality using estimates of HR in non-hospitalized and hospitalized groups were 3.68 and 2.97, respectively (Supplementary Table S9). Unobserved confounding variables have to have at least 3.68- and 2.97-fold stronger associations with all-cause mortality to explain away the effect of nirmatrelvir-ritonavir on the outcome relative to molnupiravir, which is unlikely.

4 | DISCUSSION

To the best of our knowledge, this was the first study to perform direct comparison between the effectiveness of nirmatrelvir-ritonavir and that of molnupiravir in non-hospitalized and hospitalized COVID-19 patients with T2DM. Nirmatrelvir-ritonavir was more effective than molnupiravir in risk reduction of all-cause mortality in non-hospital and hospital settings. Hence, nirmatrelvir-ritonavir could be prioritized for patients without contraindications to either antiviral agent.

To date, there is limited evidence resulting from direct comparisons of the effectiveness of nirmatrelvir-ritonavir and that of molnupiravir in COVID-19 patients with T2DM. However, our results aligned with existing indirect evidence. In the EPIC-HR trial, among the subgroup of 252 COVID-19 patients with pre-existing DM (nirmatrelvir-ritonavir: 125; placebo: 127), there was a 77% relative risk reduction in hospitalization or mortality for the nirmatrelvir-ritonavir treatment group as compared with the group receiving placebo.[16] In the MOVe-OUT trial, a total of 224 COVID-19 patients with pre-existing DM were identified (molnupiravir: 107; placebo: 117). A 9% increase in relative risk of hospitalization or all-cause mortality was found in the molnupiravir treatment group as compared with patients receiving placebo.[15] The results from the two randomized controlled trials imply a greater extent of risk reduction for nirmatrelvir-ritonavir as compared with molnupiravir.

In a recent retrospective cohort study, the effectiveness of nirmatrelvir-ritonavir and molnupiravir in non-hospitalized patients with COVID-19 and T2DM was evaluated. Nirmatrelvir-ritonavir and molnupiravir treatments were both significantly associated with all-cause mortality risk reduction (nirmatrelvir-ritonavir vs. control: HR 0.29, 95% CI 0.13–0.63; molnupiravir vs. control: HR 0.48, 95% CI 0.33–0.70) and hospitalization (nirmatrelvir-ritonavir vs. control: HR 0.71, 95% CI 0.63–0.80; molnupiravir vs. control: HR 0.71, 95% CI 0.64–0.79).[18] In that study, the database sources in Hong Kong were the same as those used in our study. Although both this previous study and our study focus on cohorts with COVID-19 infection and T2DM in Hong Kong, the differences highlight the importance of our findings. First, emulation of a hypothetical randomized trial was adopted, which reduces the biases common in observational studies.[30–32] Second, in the previous study, a treatment group (nirmatrelvir-ritonavir and molnupiravir) was compared with a non-treatment

TABLE 1 Baseline characteristics of eligible COVID-19 patients with type 2 diabetes after one-to-one propensity-score matching.

Characteristics	Non-hospitalized patients ($N = 17\,974$)			Hospitalized patients ($N = 3678$)		
	Nirmatrelvir-ritonavir ($N = 8987$)	Molnupiravir ($N = 8987$)	SMD[a]	Nirmatrelvir-Ritonavir ($N = 1839$)	Molnupiravir ($N = 1839$)	SMD[a]
Age, years; mean (SD)	72.87 (10.32)	73.82 (11.38)	0.088	77.80 (10.75)	77.97 (11.66)	0.015
Sex: male, *n* (%)	4419 (49.2)	4409 (49.1)	0.002	907 (49.3)	914 (49.7)	0.008
CCI; mean (SD)	4.12 (1.55)	4.29 (1.65)	0.107	4.93 (1.73)	5.20 (1.94)	0.149
COVID-19 vaccination, *n* (%)			0.078			0.069
Unvaccinated	585 (6.5)	698 (7.8)		250 (13.6)	283 (15.4)	
1 dose	266 (3.0)	361 (4.0)		74 (4.0)	90 (4.9)	
2 doses	1169 (13.0)	1138 (12.7)		320 (17.4)	311 (16.9)	
≥3 doses	6967 (77.5)	6790 (75.6)		1195 (65.0)	1155 (62.8)	
Duration of type 2 diabetes, years; mean (SD)	5.32 (1.92)	5.35 (1.86)	0.015	5.20 (2.06)	5.15 (2.08)	0.024
Pre-existing comorbidities, *n* (%)						
Cancer	547 (6.1)	562 (6.3)	0.007	167 (9.1)	190 (10.3)	0.042
Respiratory disease	401 (4.5)	468 (5.2)	0.035	153 (8.3)	176 (9.6)	0.044
Hypertension	7226 (80.4)	7265 (80.8)	0.011	1519 (82.6)	1494 (81.2)	0.035
Diabetes-related complications						
Macrovascular complications						
Cardiovascular disease	1235 (13.7)	1430 (15.9)	0.061	403 (21.9)	471 (25.6)	0.087
Peripheral vascular disease	39 (0.4)	86 (1.0)	0.063	22 (1.2)	42 (2.3)	0.083
Microvascular complications						
Diabetic nephropathy	25 (0.3)	43 (0.5)	0.033	6 (0.3)	14 (0.8)	0.059
Diabetic retinopathy	133 (1.5)	174 (1.9)	0.035	39 (2.1)	51 (2.8)	0.042
Diabetic neuropathy	600 (6.7)	776 (8.6)	0.074	213 (11.6)	307 (16.7)	0.147
Medication use within 90 days, *n* (%)						
Renin-angiotensin-system agents	4987 (55.5)	5013 (55.8)	0.006	993 (54.0)	996 (54.2)	0.003
Beta blockers	2640 (29.4)	2756 (30.7)	0.028	549 (29.9)	622 (33.8)	0.085
Calcium channel blockers	5513 (61.3)	5611 (62.4)	0.022	1101 (59.9)	1105 (60.1)	0.004
Diuretics	816 (9.1)	1032 (11.5)	0.079	264 (14.4)	348 (18.9)	0.123
Nitrates	755 (8.4)	923 (10.3)	0.064	200 (10.9)	257 (14.0)	0.094
Lipid-lowering agents	6979 (77.7)	7014 (78.0)	0.009	1330 (72.3)	1359 (73.9)	0.036
Insulin	900 (10.0)	1116 (12.4)	0.076	311 (16.9)	422 (22.9)	0.152
Sulphonylureas	2851 (31.7)	2877 (32.0)	0.006	599 (32.6)	572 (31.1)	0.032
Metformin	5678 (63.2)	5346 (59.5)	0.076	1019 (55.4)	969 (52.7)	0.055
DPP-4 inhibitors	1143 (12.7)	1391 (15.5)	0.079	290 (15.8)	390 (21.2)	0.140
SGLT2 inhibitors	668 (7.4)	686 (7.6)	0.008	112 (6.1)	139 (7.6)	0.058
GLP-1 agonists	79 (0.9)	112 (1.2)	0.036	2 (0.1)	14 (0.8)	0.099

Abbreviations: CCI, Charlson comorbidity index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference.

[a]SMD <0.1 indicates balance between groups.

group. The results provide evidence of the effectiveness of the two antiviral agents individually, but not of the priority of treatments when both options are available. In this study, patients who received nirmatrelvir-ritonavir treatment were compared head-to-head with those who received molnupiravir treatment. The results are therefore able to provide evidence of the benefits of nirmatrelvir-ritonavir

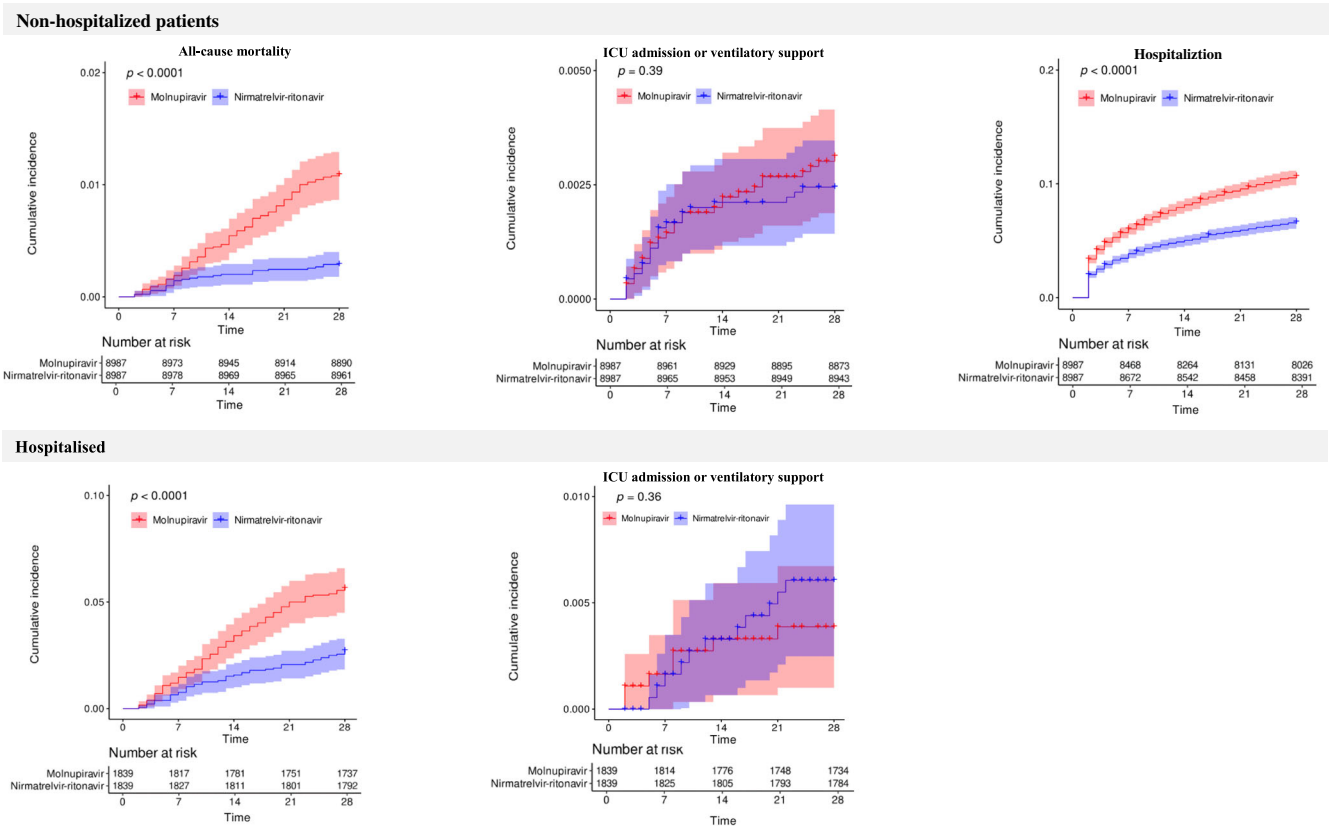

FIGURE 2 The 28-day cumulative incidence of outcomes. ICU, intensive care unit.

versus molnupiravir treatment when patients have no contraindication to either treatment. Although clinical guidelines recommend the use of nirmatrelvir-ritonavir over molnupiravir,[20–22] evidence from direct head-to-head comparison is lacking. This study was therefore important as supporting evidence for the clinical guidelines.

In view of the differences in study design and patient populations, valid conclusions from indirect comparison remain limited. In an observational study, in which direct comparison was made between the two antiviral treatments in patients with COVID-19 (with DM patients included), no significant effects were found on hospitalization (HR 0.79, 95% CI 0.61–1.02) or death (HR 1.18, 95% CI 0.58–2.39). However, the sample size of 1750 in each treatment group was relatively small and might not provide sufficient statistical power to detect differences, and the DM patients represented only 39% and 41% of the nirmatrelvir-ritonavir and molnupiravir groups, respectively.[39] In the hospitalized patients, evidence for the effectiveness of either nirmatrelvir-ritonavir or molnupiravir treatments specifically for patients with pre-existing T2DM is still lacking. In this study, on application of target trial emulation to real-world data, the direct head-to-head comparison could provide evidence of the clinical benefits of nirmatrelvir-ritonavir treatment over molnupiravir specifically for patients with T2DM in both non-hospital and hospital settings.

To date, several studies have been performed to validate the effectiveness of both nirmatrelvir-ritonavir and molnupiravir in the treatment of patients with COVID-19 in both non-hospital and hospital settings, with regard to mortality, hospitalization or progression to severe illness.[15,16,40–44] A few studies have also provided evidence of the effectiveness of both treatments in patients with DM.[18,19,45] However, the antiviral activities of nirmatrelvir-ritonavir and molnupiravir differ. While nirmatrelvir-ritonavir is a protease inhibitor targeting viral replication of SARS-CoV-2 proteases,[46] molnupiravir promotes mutations of viral RNA and impairs replication of SARS-CoV-2.[47] Furthermore, hyperglycaemia in patients with DM may activate the SARS-CoV-2 receptor to promote entry of the virus into cells,[11] affect innate and adaptive immunity, and alter inflammatory response.[12,13] Distinct mechanisms of action between the two treatments, and potential variations in the response of patients with T2DM towards SARS-CoV-2 may lead to differences in the effectiveness of these antiviral treatments.

Despite the significant risk reduction of all-cause mortality in the nirmatrelvir-ritonavir treatment group as compared with the molnupiravir treatment group, there was no significant difference in the risk of ICU admission or ventilatory support between the two oral antiviral agents. The inclusion period for subjects in this study was 16 March 2022 to 31 December 2022, which overlapped with the fifth wave of the COVID-19 epidemic in Hong Kong. The surge in cases of COVID-19 has increased the burden on public hospitals and isolation facilities, and reduced manpower in the healthcare system.[48,49] Hence, patients with COVID-19 who required ICU admission might not be able to receive appropriate medical care. Furthermore, the codes used in the

TABLE 2 Risk of outcomes for COVID-19 patients with type 2 diabetes receiving nirmatrelvir-ritonavir compared with molnupiravir.

Outcomes	Non-hospitalized patients ($N = 17\,974$)									
	Nirmatrelvir-ritonavir ($N = 8987$)				Molnupiravir ($N = 8987$)					
	Events	Rate, %	Follow-up, days	Incidence rate, per 10 000 person days	Events	Rate, %	Follow-up, days	Incidence rate, per 10 000 person days	ARR (95% CI), %	Adjusted HR (95% CI)[a]
Effectiveness outcome										
All-cause mortality	26	0.29	251 199	1.04 (0.68, 1.52)	98	1.09	250 317	3.92 (3.18, 4.77)	0.80 (0.56, 1.04)	0.47 (0.30, 0.73)
ICU admission or ventilatory support	22	0.24	250 820	0.88 (0.55, 1.33)	28	0.31	249 925	1.12 (0.74, 1.62)	0.07 (−0.09, 0.22)	1.01 (0.57, 1.80)
Hospitalization	597	6.64	240 065	24.87 (22.91, 26.95)	957	10.65	232 916	41.09 (38.53, 43.78)	4.01 (3.19, 4.83)	0.73 (0.66, 0.82)
	Hospitalized patients ($N = 3678$)									
	Nirmatrelvir-ritonavir ($N = 1839$)				Molnupiravir ($N = 1839$)					
Effectiveness outcome										
All-cause mortality	50	2.72	50 781	9.85 (7.31, 12.98)	104	5.66	49 931	20.83 (17.02, 25.24)	2.94 (1.65, 4.23)	0.56 (0.40, 0.80)
ICU admission or ventilatory support	11	0.60	50 638	2.17 (1.08, 3.89)	7	0.38	49 837	1.40 (0.56, 2.89)	-0.22 (−0.67, 0.23)	1.47 (0.56, 3.87)

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a]HRs were obtained from Cox proportional hazard regression adjusted by sex, age, Charlson Comorbidity Index, vaccination status, pre-existing comorbidities and medication use within 90 days at baseline.

TABLE 3 Subgroup analysis for all-cause mortality.

Subgroup	Events	Rate, %	Follow-up, days	Incidence rate, per 10 000 person days	Events	Rate, %	Follow-up, days	Incidence rate, per 10 000 person days	ARR (95% CI), %	Adjusted HR (95% CI)[a]	*p* value for interaction
	Non-hospitalized patients (*N* = 17 974)										
	Nirmatrelvir-ritonavir (*N* = 8987)				**Molnupiravir (*N* = 8987)**						
All-cause mortality											
Age											0.905
<70 years	1	0.03	92 801	0.11 (0.003, 0.60)	3	0.10	87 301	0.34 (0.07, 1.00)	0.07 (−0.06, 0.19)	0.15 (0.01, 1.52)	
≥70 years	25	0.44	158 398	1.58 (1.02, 2.33)	95	1.62	163 016	5.83 (4.71, 7.12)	1.18 (0.81, 1.54)	0.47 (0.3, 0.75)	
Sex											0.298
Male	16	0.36	123 455	1.30 (0.74, 2.10)	45	1.02	122 887	3.66 (2.67, 4.90)	0.66 (0.31, 1.00)	0.56 (0.31, 1.02)	
Female	10	0.22	127 744	0.78 (0.38, 1.44)	53	1.16	127 430	4.16 (3.12, 5.44)	0.94 (0.60, 1.28)	0.35 (0.17, 0.71)	
CCI											0.836
<4	1	0.03	87 301	0.11 (0.003, 0.64)	3	0.11	79 489	0.38 (0.08, 1.10)	0.08 (−0.06, 0.21)	0.32 (0.03, 3.07)	
≥4	25	0.43	163 898	1.53 (0.99, 2.25)	95	1.55	170 828	5.56 (4.50, 6.80)	1.12 (0.77, 1.47)	0.48 (0.3, 0.76)	
COVID-19 vaccination											0.742
<2 doses	5	0.85	16 283	3.07 (1.00, 7.17)	26	3.72	19 169	13.56 (8.86, 19.87)	2.87 (1.28, 4.46)	0.46 (0.17, 1.28)	
≥2 doses	21	0.25	234 916	0.89 (0.55, 1.37)	72	0.87	231 148	3.11 (2.44, 3.92)	0.62 (0.39, 0.85)	0.46 (0.28, 0.77)	
	Hospitalized patients (*N* = 3678)										
	Nirmatrelvir-ritonavir (*N* = 1839)				**Molnupiravir (*N* = 1839)**						
All-cause mortality											
Age											0.565
<70 years	3	0.87	9642	3.11 (0.64, 9.09)	13	3.42	10 420	12.48 (6.64, 21.33)	2.55 (0.48, 4.63)	0.14 (0.03, 0.64)	
≥70 years	47	3.15	41 139	11.42 (8.39, 15.19)	91	6.24	39 511	23.03 (18.54, 28.28)	3.09 (1.57, 4.61)	0.62 (0.43, 0.89)	
Sex											0.994
Male	26	2.87	25 027	10.39 (6.79, 15.22)	54	5.91	24 850	21.73 (16.32, 28.35)	3.04 (1.17, 4.92)	0.56 (0.34, 0.90)	
Female	24	2.58	25 754	9.32 (5.97, 13.87)	50	5.41	25 081	19.94 (14.80, 26.28)	2.83 (1.05, 4.61)	0.58 (0.35, 0.96)	
CCI											0.747
<4	2	0.72	7742	2.58 (0.31, 9.33)	3	1.08	7755	3.87 (0.80, 11.31)	0.36 (−1.21, 1.93)	0.22 (0.02, 2.15)	
≥4	48	3.07	43 039	11.15 (8.22, 14.79)	101	6.47	42 176	23.95 (19.51, 29.10)	3.40 (1.90, 4.89)	0.56 (0.39, 0.79)	
COVID-19 vaccination											0.608
<2 doses	10	4.00	6860	14.58 (6.99, 26.81)	21	7.42	7605	27.61 (17.09, 42.21)	3.42 (−0.48, 7.32)	0.68 (0.30, 1.53)	
≥2 doses	40	2.52	43 921	9.11 (6.51, 12.40)	83	5.33	42 326	19.61 (15.62, 24.31)	2.81 (1.46, 4.17)	0.53 (0.36, 0.78)	

Abbreviations: ARR, absolute risk reduction; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.

[a]HRs were obtained from Cox proportional hazard regression adjusted by sex, age, CCI and vaccination status, pre-existing comorbidities and medication use within 90 days at baseline.

database to determine use of ventilators might also have led to underdiagnosis, and the data on ICU admission and ventilatory support might not be fully representative. In view of this, other measures could be used in place of ICU admission or ventilatory support to evaluate the effectiveness of nirmatrelvir-ritonavir and molnupiravir on reducing the severity of COVID-19.

Careful interpretation of our findings is required. Patients with T2DM are commonly diagnosed with comorbidities such as cardiovascular disease and renal insufficiency.[50] The interaction between nirmatrelvir-ritonavir and existing medications for cardiovascular comorbidities in patients with T2DM has to be taken into consideration.[51] Nirmatrelvir-ritonavir is also not recommended for patients with severe liver or renal impairment.[33] Therefore, taking the medical history of the patients into consideration, molnupiravir may be a more suitable option for treating patients with COVID-19.

To the best of our knowledge, this is the first study to conduct a direct comparison of the effectiveness of molnupiravir and nirmatrelvir-ritonavir in non-hospitalized and hospitalized COVID-19 patients with pre-existing T2DM. While indirect comparison among studies may not be applicable, our findings provide the comparative effectiveness based on direct evidence using data from a territory-wide electronic health records database in Hong Kong, which represents populations in local non-hospital and hospital settings. Target trial emulation could also address some typical challenges associated with observational studies, such as immortal time and selection biases.[30–32]

Nevertheless, this study has several limitations. First, since the date of onset of COVID-19 symptoms was unavailable, the date of COVID-19 infection was proxied with the date of first positive PCR or rapid antigen test result. Second, only patients with recorded positive PCR or rapid antigen test result were identified as COVID-19 patients. Therefore, people who did not report or were unaware of their infection, or who performed the test after experiencing COVID-19 symptoms for a period of time may affect the representativeness of the data. Third, there are confounding variables which are not available in the electronic health records dataset. Hence, potential residual bias could not be completely eliminated. Fourth, data on treatment adherence were not available in the database. Fifth, as patients with T2DM were specifically selected for the study, these patients might have comorbidities which could have affected the rates of mortality, ICU admission or ventilatory support, and hospitalization. Sixth, information on mortality and hospitalization caused by COVID-19 was not available. There was no further identification of the cause of the effectiveness outcomes. Last, due to the design of observational studies, residual confounding and confounding by indication may still exist.

In conclusion, the findings from this target trial emulation suggest nirmatrelvir-ritonavir is a more effective treatment than molnupiravir in reducing the risk of all-cause mortality of COVID-19 patients with T2DM in both non-hospital and hospital settings. Hence, the use of nirmatrelvir-ritonavir may be preferred over molnupiravir for patients with no contraindications to these antiviral agents. Further studies are required to examine the comparative effectiveness of the treatments to support management of this specific population.

AUTHOR CONTRIBUTIONS

Concept and design: Eric Y. F. Wan, Zoey C. T. Wong, Ian C. K. Wong and Esther W. Y. Chan. Acquisition of data: Ian C. K. Wong. Analysis or interpretation of data: Eric Y. F. Wan, Zoey C. T. Wong, Vincent K. C. Yan, Francisco T. T. Lai, Celine S. L. Chui, Xue Li, Ian C. K. Wong and Esther W. Y. Chan. Drafting of the manuscript: Eric Y. F. Wan, Zoey C. T. Wong and Vincent K. C. Yan. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Eric Y. F. Wan, Zoey C. T. Wong and Vincent K. C. Yan. Administrative, technical or material support: Ian C. K. Wong and Esther W. Y. Chan. Supervision: Ian C. K. Wong and Esther W. Y. Chan.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are not available as the data custodians (the Hospital Authority and the Department of Health of Hong Kong SAR) have not given permission for sharing due to patient confidentiality and privacy concerns. Local academic institutions, government departments, or non-governmental organizations may apply for the access to data through the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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