Impact of the use of oral antiviral agents on the risk of hospitalization in community COVID-19 patients

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ABSTRACT

Background

We examined the effectiveness of molnupiravir and nirmatrelvir/ritonavir in reducing hospitalization and deaths in a real-world cohort of non-hospitalized COVID-19 patients.

Methods

This was a territory-wide retrospective cohort study in Hong Kong. Non-hospitalized COVID-19 patients who attended designated outpatient clinics between 16 February and 31 March 2022 were identified. Patients hospitalized on the day of the first clinic appointment or used both oral antivirals were excluded. The primary endpoint was hospitalization. The secondary endpoint was a composite of intensive care unit admission, invasive mechanical ventilation use, and/or death.

Results

Of 93,883 patients, 83,154 (88.6%), 5,808 (6.2%), and 4,921 (5.2%) were oral antiviral non-users, molnupiravir users, and nirmatrelvir/ritonavir users respectively. Compared to non-users, oral antiviral users were older and had more comorbidities, lower complete vaccination rate, and more hospitalizations in the previous year. Molnupiravir users were older, and had more comorbidities, lower complete vaccination rate, and more hospitalizations in the previous year than nirmatrelvir/ritonavir users. At a median follow-up of 30 days, 1,931 (2.1%) patients were hospitalized and 225 (0.2%) patients developed the secondary endpoint. After propensity score weighting, nirmatrelvir/ritonavir use (weighted hazard ratio 0.79, 95%CI 0.65-0.95, *P*=0.011) but not molnupiravir use (weighted hazard ratio 1.17, 95%CI 0.99-1.39, *P*=0.062) was associated with a reduced risk of hospitalization than non-users. The use of molnupiravir or nirmatrelvir/ritonavir was not associated with a lower risk of the secondary endpoint as compared to non-users.

Conclusion

Use of nirmatrelvir/ritonavir but not molnupiravir was associated with a reduced risk of hospitalization in real-world non-hospitalized COVID-19 patients.

Keywords: SARS-CoV-2, hospital admission, death, molnupiravir, nirmatrelvir/ritonavir

Abbreviations: CDARS = Clinical Data Analysis and Reporting System, CI = confidence interval, DM = diabetes mellitus, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IMV = invasive mechanical ventilation, HR = hazard ratio, ICU = intensive care unit, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

INTRODUCTION

The landscape of development of therapeutics and preventive strategies for COVID-19 has evolved rapidly since the start of the COVID-19 pandemic, including the treatment of severe disease in hospitalized patients, and vaccine platforms for the prevention of infection and severe disease.[1, 2] The latest breakthroughs in therapeutics emphasized early treatment for prevention of progression to severe disease among non-hospitalized patients.[3] Two oral antiviral agents, molnupiravir and nirmatrelvir/ritonavir, have recently been authorized or supported to be used worldwide for the treatment of mild to moderate COVID-19 in adults at risk for progressing to severe COVID-19,[4] and non-hospitalized patients at risk of hospitalization or progression to severe disease.[5, 6]

The treatment authorizations and guidelines were mostly based on a single randomized trial for each of the drugs on individuals with mild to moderate COVID-19 and one or more risk factors for progression to severe disease within five days of symptom onset. The MOVe-OUT study showed that the molnupiravir group had a lower risk of hospitalization or death than placebo (6.8% vs 9.7%), or relative risk reduction of 30% and number needed to treat (NNT) of 34.[7] In the EPIC-HR study, the nirmatrelvir/ritonavir group had a lower risk of hospitalization or death (0.72% vs 6.53%), or relative risk reduction of 89% and NNT of 17.[8]

However, there is a paucity of knowledge on whether these trial data would translate into similar real-world effectiveness. The studied populations in these trials were relatively young (median age in the 40s), and the most frequently reported risk factor for progression to severe disease was obesity (reported in 74% and 81% of the two trials respectively).[7, 8] Real-world data include

older patients with different comorbidities.[9] It is important to understand the real-world effectiveness of oral antivirals for public health authorities to determine the most cost-effective strategies for averting severe disease and reducing healthcare burden by targeting appropriate populations for treatment.[10] In this territory-wide study, we aimed to determine the real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir in reducing hospitalization and deaths among non-hospitalized COVID-19 patients.

METHODS

Setting and Study Design

A territory-wide retrospective cohort study was performed using data from Clinical Data Analysis and Reporting System (CDARS), an electronic healthcare database managed by Hospital Authority, Hong Kong.[11] CDARS captures de-identified data of patients' demographic, death, diagnoses, procedures, drug prescription and dispensing history, and laboratory results from all public hospitals and clinics in Hong Kong, and represents inpatient and outpatient data of around 80% of the 7.4-million population. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding was adopted in CDARS; it is found 99% accurate to identify medical conditions with reference to clinical, laboratory, imaging, and endoscopy results from electronic medical records.[12] Territory-wide studies on COVID-19 have previously been conducted using CDARS.[12, 13]

Patients

COVID-19 patients who attended COVID-19 designated clinics in Hong Kong between 16 February 2022 and 31 March 2022 were identified by appointment records. Details on designated clinics were described in Supplementary Methods. Molnupiravir and nirmatrelvir/ritonavir were

started to be prescribed to elderly and individuals with high-risk factors and incomplete COVID-19 vaccination within five days of symptom onset in designated clinics on 12 March 2022 and 16 March 2022 respectively, after these drugs had become available (Supplementary Table 1). Patients hospitalized on the day of the first appointment at designated clinic and/or used both molnupiravir and nirmatrelvir/ritonavir were excluded. Patients were followed until the occurrence of the clinical endpoint, death, date of data retrieval (25 April 2022), and up to 30 days, whichever came first. The study protocol was approved by the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (Reference number: 2021.239).

Data were retrieved on 26 April 2022. Baseline date was defined as the date of the first appointment at designated clinic. We retrieved data on date of birth, sex, hospitalization, diagnoses, procedures, and use of molnupiravir, nirmatrelvir/ritonavir, and other relevant concomitant drugs before baseline and during follow-up. We also collected patients' laboratory parameters including hemoglobin A_{1c}, fasting plasma glucose, C-reactive protein, international normalized ratio, complete blood picture, liver biochemistries, renal function tests, and COVID-19 PCR tests.

Definitions

The primary endpoint was hospital admission. The secondary endpoint was a composite endpoint of intensive care unit (ICU) admission, use of invasive mechanical ventilation (IMV), and/or death. Hospital admission was defined as hospitalization with a stay of more than 1 day. Date and cause of death were ascertained using data from CDARS and Hong Kong Death Registry. IMV use was defined by ICD-9-CM procedure codes (96.04-96.05, 96.7). Definition of

comorbidities and complete vaccination were described in Supplementary Methods and Supplementary Table 2.

Statistical analysis

Data were analyzed using R software (version 4.1.2). Continuous variables were expressed in mean ± standard deviation or median (25^{th} percentile - 75^{th} percentile [P25-P75]), as appropriate, while categorical variables were presented as frequency (percentage). Qualitative and quantitative differences between groups were analyzed by Chi-square test or Fisher's exact tests for categorical parameters and one-way ANOVA or Kruskal-Wallis test for continuous parameters, as appropriate. Propensity score (PS), the conditional probability of using nirmatrelvir/ritonavir given patients' clinical characteristics, was estimated among nirmatrelvir/ritonavir users, molnupiravir users, and oral antiviral non-users to control for confounders and reduce selection bias. Details of PS and weighted Cox model were described in Supplementary Methods. Cumulative incidence with 95% confidence interval (CI) of the primary and secondary endpoints of the three groups was estimated by Kaplan-Meier method. Robust (empirical) variance estimates were obtained to calculate 95% CI of the weighted hazard ratio (wHR). Two subgroup analyses were performed in high-risk patients aged 60 years or above or aged below 60 years with at least one comorbidity, and patients above and below 70 years which represented two populations with different complete vaccination rates. All statistical tests were two-sided. Statistical significance was taken as $P<0.05$.

RESULTS

Demographic Characteristics

We identified 94,167 COVID-19 patients with an appointment at designated clinics from 16 February 2022 to 31 March 2022. We excluded 271 patients who were hospitalized on the day of the first appointment at the designated clinic, and 13 patients who received both molnupiravir and nirmatrelvir/ritonavir; thus 93,883 patients (83,154 oral antiviral non-users, 5,808 molnupiravir users, and 4,921 nirmatrelvir/ritonavir users) were included in the analysis (Supplementary Figure 1); 10,569 (98.5%) and 10,656 (99.3%) of the oral antivirals were prescribed on the same date and within the first 2 days of baseline date respectively. At baseline, compared to oral antiviral non-users, molnupiravir or nirmatrelvir/ritonavir users were older, and had more comorbidities including digestive diseases, diabetes mellitus (DM), history of malignant tumor, more hospital admission in the previous year, and lower complete vaccination rate (Table 1). Compared to nirmatrelvir/ritonavir users, molnupiravir users were older and had more cardiovascular diseases, DM, cerebrovascular events, respiratory diseases, and kidney diseases, more hospital admission in the previous year, and lower complete vaccination rate (Table 1).

Clinical outcomes

At a median (P25-P75) follow-up of 30 (30-30) days, 1,931 (2.1%) patients were hospitalized; 1,322 (1.6%), 437 (7.5%) and 172 (3.5%) oral antiviral non-users, molnupiravir users, and nirmatrelvir/ritonavir users were hospitalized respectively. Among 1,931 hospitalized patients, 558 (28.9%) received oxygen therapy; 179 (9.3%) used remdesivir. Among 93,883 patients, 225 (0.2%) patients developed the secondary endpoint in 30 days, *i.e.* ICU admission, IMV use,

and/or death; 151 (0.2%), 53 (0.9%), and 21 (0.4%) oral antiviral non-users, molnupiravir users, and nirmatrelvir/ritonavir users developed the secondary endpoint respectively.

Propensity score weighting analysis

After PS weighting, the clinical characteristics were balanced between nirmatrelvir/ritonavir users, molnupiravir users, and oral antiviral non-users (Table 2). Molnupiravir use was not associated with a reduced risk of hospital admission than oral antiviral non-users (wHR 1.17, 95% CI 0.99-1.39, *P*=0.062). Nirmatrelvir/ritonavir use was associated with a lower risk of hospital admission than oral antiviral non-users (wHR 0.79, 95% CI 0.65-0.95, *P*=0.011) and molnupiravir users (wHR 0.67, 95% CI 0.55-0.81, *P*<0.001) (Table 3). The 30-day cumulative incidence (95% CI) of hospital admission was 4.5% (4.0%-5.0%), 5.2% (4.6%-5.9%), and 3.6% (3.1%-4.1%) in non-users, molnupiravir users, and nirmatrelvir/ritonavir users respectively (Figure 1A). Similar results were found in patients aged 60 years or above or aged below 60 years with at least one comorbidity (Table 3, Supplementary Table 3, and Figure 2A). In patients aged above and below 70 years, the complete vaccination rate was 30% and 60% respectively (Supplementary Tables 4-5). Similar associations between use of nirmatrelvir/ritonavir (wHR 0.78 and 0.77) and molnupiravir (wHR 1.15 and 1.07) with hospital admission were observed (Supplementary Table 6).

Molnupiravir (wHR 1.12, 95% CI 0.68-1.82, *P*=0.663) or nirmatrelvir/ritonavir use (wHR 0.81, 95% CI 0.47-1.39, *P*=0.448) were not associated with a lower risk of death/ICU admission/IMV use than oral antiviral non-users. Also, nirmatrelvir/ritonavir use was not associated with a lower risk of death/ICU admission/IMV use than molnupiravir users (weighted HR 0.73, 95% CI 0.41-

1.27, *P*=0.265) (Table 3). The 30-day cumulative incidence (95% CI) of death/ICU admission/IMV use was 0.5% (0.4%-0.7%), 0.6% (0.4%-0.9%), and 0.4% (0.3%-0.7%) in non-users, molnupiravir users, and nirmatrelvir/ritonavir users respectively (Figure 1B). Similar findings were observed in patients aged 60 years or above or aged below 60 years with at least one comorbidity (Table 3, Supplementary Table 3, and Figure 2B). In patients aged above and below 70 years, similar associations between use of nirmatrelvir/ritonavir (wHR 0.89 and 0.55) and molnupiravir (wHR 1.08 and 0.97) with death/ICU admission/IMV use were observed (Supplementary Table 6).

DISCUSSION

This study describes the real-world effectiveness of the two COVID-19 oral antivirals amidst the peak of an outbreak with omicron variant infections in a densely populated city. Compared to no antiviral treatment, nirmatrelvir/ritonavir significantly reduced hospital admission by more than 20%, whereas molnupiravir did not reduce hospital admission of community COVID-19 patients. Neither of the drugs reduced the risk of adverse clinical outcomes, namely death, ICU admission, and IMV use.

At a critical time witnessing the rapid global spread of the omicron variant, molnupiravir and nirmatrelvir/ritonavir were approved for outpatient treatment of patients with mild to moderate disease and at risk for disease progression, to reduce the risk of hospital admission and deaths if administered early to high-risk subjects.[14, 15] In clinical trials, nirmatrelvir/ritonavir demonstrated a greater relative risk reduction in hospitalization and death than molnupiravir compared to placebo.[7, 8] Yet there have not been any head-to-head comparisons between the

two drugs. The unique situation in Hong Kong with the availability of both drugs of different antiviral mechanisms at the same time facilitated their comparisons in real-world setting. The apparent lack of effectiveness in reducing hospitalization by molnupiravir might partly be related to its availability in earlier days when our local guideline limited its use to patients at highest baseline risk, namely advanced age (≥70 years) and unvaccinated status. Moreover, molnupiravir was preferentially prescribed to more frail patients with multiple comorbidities and polypharmacy than those who received nirmatrelvir/ritonavir, perhaps because of the multiple drug-drug interactions associated with the latter.[16, 17] When nirmatrelvir/ritonavir became available, the guideline relaxed the use of both oral antivirals in older patients regardless of vaccination status and in younger patients with comorbidities. This explains why molnupiravir users was older and had more comorbidities than nirmatrelvir/ritonavir users and non-users. However, we have balanced the differences in host characteristics among the three groups using PS weighting, and were not able to observe any significant association between molnupiravir use and hospitalization in the weighted analyses; residual unmeasured confounding that was not adjusted by PS might have obscured an impact of molnupiravir on reduced hospitalization risk. Only 0.2% of patients developed death/ICU admission/IMV use in the study. The low event rate led to the wider CIs of the HRs. Yet, the direction and magnitude of the HRs for death/ICU admission/IMV use were similar to those for the primary outcome. The MOVe-OUT trial has been criticized for overestimated treatment effects in the interim analysis, lack of explanation for post-interim period data favoring placebo, and wide differences in outcomes among participating countries.[18, 19]

In the MOVe-OUT and EPIC-HR trials, 60% and 98% of the participants were infected by the

delta variant respectively.[7, 8] Our territory-wide, real-world cohort was different. The rapid surge of COVID-19 in the first quarter of 2022 in Hong Kong was primarily related to the highly transmissible nature of the omicron variant.[20] Although these two drugs were shown to retain antiviral activity against omicron variant *in vitro*,[21] their effectiveness in clinical settings remains to be established, as the omicron variant possesses higher transmissibility and reduced pathogenicity than earlier variants.[22] Hong Kong has experienced the fifth wave of COVID-19 since 31 December 2021, with a cumulative number of 1,376,651 confirmed cases by 8 August 2022 (Supplementary Figure 2).[20] The share of omicron variant rose rapidly from 93% to 100% since early January 2022.[23] This would be a suitable setting to determine the real-world impact of oral antivirals in COVID-19 infections caused predominantly by omicron. Our current observations fortify the real-world impact of these two novel oral antivirals, as the omicron variant has been the predominant strain worldwide since late 2021. Global COVID-19 cases surpassed 500 million in early April, as the highly contagious BA.2 sub-omicron variant surges in many countries in Europe and Asia, including China.

The two landmark trials enrolled solely unvaccinated participants. As vaccination and booster rates are rising in all countries, further study is needed for their effectiveness among partially or fully vaccinated individuals with breakthrough infections.[4] The proportion of Hong Kong population who received at least one dose of SARS-CoV-2 vaccine rose from 65% to 93.1% from 31 December 2021 to 8 August 2022.[24] More than 80% of the population have completed the second dose by March 2022; yet the coverage of third dose remained below 50%.[24] A study from Israel involving patients with at least one risk factor for disease progression and an overall adequate vaccination rate of 75% showed that nirmatrelvir/ritonavir had a 46% reduced

relative risk of progression to severe disease or death.[25] Another study from Hong Kong involving non-hospitalized patients with 54% being fully vaccinated showed that nirmatrelvir/ritonavir reduced hospitalization by 31%, while molnupiravir was not associated with a lower hospitalization rate.[26] Effectiveness of nirmatrelvir/ritonavir was not affected by vaccination status in these two studies. Similarly, in our study, the associations of oral antiviral use and primary and secondary endpoints were similar between those below and above 70 years, who represented different vaccination rates. While ongoing trials will provide more data in vaccinated populations infected with omicron variant,[27, 28] our study and theirs supported the use of nirmatrelvir/ritonavir in preventing hospitalization in vaccinated populations with risk factors for disease progression. The established risk factors, namely advanced age and presence of comorbidities, facilitate prioritized referral of community COVID-19 patients to designated clinics and timely use of oral antiviral treatment to avoid hospitalization. Our findings would facilitate the clinical management and resource allocation for appropriate use of these oral antivirals amidst the COVID-19 outbreak.

The strengths of our study include a territory-wide, real-world cohort that covers 100% of the designated clinic services and more than 95% of the in-patient service for COVID-19 patients. Our real-world cohort represents a wider spectrum of patients such that the findings are more representative of individuals encountered in daily clinical practice than those enrolled in clinical trials. Our study has a few limitations. First, COVID-19 patients untreated with oral antivirals were much younger than the treated ones due to indication bias. We compensated this major discrepancy by various approaches, including PS weighting, which rendered age to be very well balanced. Second, many patients might not be seen at designated clinics or hospitalized at the

peak of the fifth wave because of the huge numbers of confirmed cases (up to a peak of 70,000 confirmed cases a day), and this might lead to fewer hospital admissions than it should have been.[29] We believe this would have affected patients prescribed and not prescribed oral antivirals similarly if they were infected at the same time during the fifth wave. Therefore, the day from the start of operation of designated clinics was balanced among the groups by PS weighting to reduce bias due to varying hospital admission thresholds throughout the fifth wave. Third, ascertainment bias may affect the reliability of study due to inaccurate entry of certain diagnosis codes for comorbidities. We minimized this bias by including laboratory and medication data for certain diagnoses such as DM and hypertension. Fourth, we did not analyze patients who resided in aged home, whose vaccination rate was about 20-50%.[30, 31] Community outreach teams prescribed either of the two oral antivirals if clinically indicated. The patients did not need to attend designated clinic. Thus, another study is warranted to evaluate the effectiveness of the two oral antivirals in these frailer patients. Fifth, there might be a difference in the time from symptom onset to baseline date between users and non-users of COVID-19 oral antiviral. Also, missing data on hemoglobin A_{1c}, body mass index, and other laboratory parameters existed as they are not routinely measured at designated clinics. As these data were not available, we did not adjust for these possible confounding factors in our analyses. Sixth, the vaccination data were only available at population level. Thus, we included the background vaccination rate of each patient at baseline as the corresponding vaccination rate in the Hong Kong population of the same age and gender.

In conclusion, this territory-wide, real-world study reported the effectiveness of the two oral antiviral agents for COVID-19 amidst the peak of an outbreak with omicron variant infections in

one of the most densely populated cities. While nirmatrelvir/ritonavir reduced hospital admission by more than 20%, molnupiravir appeared not to be able to reduce hospital admission of community COVID-19 patients. Given the ongoing outbreak worldwide, we have to update our management guidelines for community COVID-19 patients and prioritize the use of these agents to those who would benefit from it. Health authorities should allocate adequate resources, in particular sufficient outpatient clinic settings and timely use of antiviral treatment, based on the trajectories of the numbers of confirmed cases for upcoming waves well ahead to avoid collapse of the healthcare systems by reducing hospital admission as much as possible.

NOTES

Authorship Statement

All authors were responsible for the study concept and design. Grace Wong, Terry Yip, Mandy Lai, Yee-Kit Tse, and Grace Lui were responsible for the acquisition and analysis of data, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the interpretation of data, the drafting, and critical revision of the manuscript for important intellectual content.

Source of Funding

None declared.

Declaration of Interests

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences. Grace Lui has served as an advisory committee member for Gilead, Merck, and GSK, speaker for Merck, Pfizer, and Gilead, and received research grant from Gilead, Merck, and GSK. Vincent Wong has served as a consultant or advisory committee member for 3V-BIO, AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk,

Pfizer, ProSciento, Sagimet Biosciences, and TARGET PharmaSolutions; and a speaker for Bristol-Myers Squibb, Abbott, AbbVie, Echosens, Gilead Sciences, Merck, and Novo Nordisk. He has received a research grant from Gilead Sciences, and is a cofounder of Illuminatio Medical Technology Limited.

Henry Chan has served as an Independent Non-Executive Director for Shanghai Henlius Biotech Inc; as an advisory board member for Aligos, Aptorum, Arbutus, Hepion, Janssen, Gilead, Glaxo-Smith-Kline, Roche, Vaccitech, Virion Therapeutics, and Vir Biotechnology; and as a speaker for Gilead, Roche, and Viatris.

Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen, and as a speaker for Abbott, Abbvie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen, and Roche. She has also received a research grant from Gilead Sciences.

David Hui is an advisory committee member for Roche (personal fees). Elsie Hui reports grants from Merck, and GSK; is an advisory committee member for Merk, Gilead, Sanofi Pasteur, and GSK, and speaker for Merck and Gilead sciences.

The other authors declare that they have no competing interests.

REFERENCES

1. Consortium WHOST, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384(6): 497-511.
2. Krammer F. SARS-CoV-2 vaccines in development. Nature **2020**; 586(7830): 516-27.
3. Gandhi RT, Malani PN, Del Rio C. COVID-19 Therapeutics for Nonhospitalized Patients. JAMA **2022**; 327(7): 617-8.
4. Dal-Re R, Becker SL, Bottieau E, Holm S. Availability of oral antivirals against SARS-CoV-2 infection and the requirement for an ethical prescribing approach. Lancet Infect Dis **2022**; 22(8): e231-e8.
5. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis **2020**.
6. World Health Organization. Therapeutics and COVID-19: living guideline. Website: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.3. Accessed on 9 August 2022.
7. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med **2022**; 386(6): 509-20.
8. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med **2022**; 386(15): 1397-408.
9. Roth GA, Emmons-Bell S, Alger HM, et al. Trends in Patient Characteristics and COVID-19 In-Hospital Mortality in the United States During the COVID-19 Pandemic. JAMA Netw Open **2021**; 4(5): e218828.
10. Jo Y, Kim SB, Radnaabaatar M, et al. Model-based cost-effectiveness analysis of oral antivirals against SARS-CoV-2 in Korea. Epidemiol Health **2022**; 44: e2022034.
11. Cheung NT, Fung V, Chow YY, Tung Y. Structured data entry of clinical information for documentation and data collection. Stud Health Technol Inform **2001**; 84(Pt 1): 609-13.
12. Lui GC, Yip TC, Wong VW, et al. Significantly Lower Case-fatality Ratio of Coronavirus Disease 2019 (COVID-19) than Severe Acute Respiratory Syndrome (SARS) in Hong Kong-A Territory-Wide Cohort Study. Clin Infect Dis **2021**; 72(10): e466-e75.
13. Yip TC, Wong VW, Lui GC, et al. Current and Past Infections of HBV Do Not Increase Mortality in Patients With COVID-19. Hepatology **2021**; 74(4): 1750-65.
14. Saravolatz LD, Depcinski S, Sharma M. Molnupiravir and Nirmatrelvir-Ritonavir: Oral COVID Antiviral Drugs. Clin Infect Dis **2022**.
15. Hui DSC, Zumla A. Advances in the epidemiology, clinical features, diagnosis, clinical management and prevention of coronavirus disease 2019. Curr Opin Pulm Med **2022**; 28(3): 166-73.
16. Kabinger F, Stiller C, Schmitzova J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol **2021**; 28(9): 740-6.
17. Ahmad B, Batool M, Ain QU, Kim MS, Choi S. Exploring the Binding Mechanism of PF-07321332 SARS-CoV-2 Protease Inhibitor through Molecular Dynamics and Binding Free Energy Simulations. Int J Mol Sci **2021**; 22(17).
18. Thorlund K, Sheldrick K, Meyerowitz-Katz G, Singh S, Hill A. Making Statistical Sense of the Molnupiravir MOVe-OUT Clinical Trial. Am J Trop Med Hyg **2022**; 106(5): 1301-4.

19. De Anda C, Johnson MG, Pedley A. Molnupiravir for Covid-19 in Nonhospitalized Patients. Reply. N Engl J Med **2022**; 386(13): e32.
20. Centre for Health Protection of the Department of Health; and the Hospital Authority. Statistics on 5th Wave of COVID-19. Website: https://www.covidvaccine.gov.hk/pdf/5th_wave_statistics.pdf. Accessed on 9 August 2022.
21. Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. Antiviral Res **2022**; 198: 105252.
22. Balint G, Voros-Horvath B, Szechenyi A. Omicron: increased transmissibility and decreased pathogenicity. Signal Transduct Target Ther **2022**; 7(1): 151.
23. Our World in Data. Share of SARS-CoV-2 sequences that are the omicron variant, Dec 13, 2021 to Mar 21, 2022. Website: https://ourworldindata.org/grapher/covid-cases-omicron?tab=chart&country=~HKG. Accessed on 9 August 2022.
24. HKSAR government. Hong Kong Vaccination Dashboard. Website: https://www.covidvaccine.gov.hk/en/dashboard. Accessed on 9 August 2022.
25. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients. Clin Infect Dis **2022**.
26. Wong CK, Au IC, Lau KT, Lau EH, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir against mortality, hospitalization, and in-hospital outcomes among community-dwelling, ambulatory COVID-19 patients during the BA.2.2 wave in Hong Kong: an observational study. medRxiv 2022.05.26.22275631 [Preprint]. May 26, 2022. Available from: https://doi.org/10.1101/2022.05.26.22275631.
27. University of Oxford. Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC). https://www.panoramictrial.org/. Accessed on 9 August 2022.
28. Pfizer. Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR). https://clinicaltrials.gov/ct2/show/NCT05011513. Accessed on 9 August 2022.
29. Centre for Health and Protection. Health Advice for Persons Tested Positive / Preliminarily Positive for COVID-19 and Pending Admission to a Hospital or Isolation Facility. Website: https://www.coronavirus.gov.hk/pdf/healthadvice_testpos_ENG.pdf. Accessed on 9 August 2022.
30. Bloomberg. Hong Kong's Nursing Homes Are Unvaccinated Hotbeds of Covid. Website: https://www.bloomberg.com/news/articles/2022-03-03/hong-kong-s-nursing-homes-are-unvaccinated-hotbeds-of-covid. Accessed on 9 August 2022.
31. HKSAR government. Overall first-dose COVID-19 vaccination rate of RCHEs and RCHDs rises to 84 per cent on 11 May 2022 (with photos/video). Website: https://www.info.gov.hk/gia/general/202205/11/P2022051100590.htm. Accessed on 9 August 2022.

Table 1. Baseline clinical characteristics of the 93,883 COVID-19 patients who attended the designated clinics in Hong Kong from 16 February 2022 to 31 March 2022.

Clinical characteristics	All N=93,883	COVID-19 oral antiviral non-users N=83,154	Use of molnupiravir N=5,808	Use of nirmatrelvir/ ritonavir N=4,921	*P* value
Age (years)	49.2 ± 21.8	46.1 ± 20.8	75.4 ± 12.1	70.8 ± 12.1	<0.001
Male sex (n, %)	41,656 (44.4)	36,706 (44.1)	2,703 (46.5)	2,247 (45.7)	<0.001
Comorbidities (n, %)					
Cardiovascular diseases	4,612 (4.9)	3,852 (4.6)	544 (9.4)	216 (4.4)	<0.001
- **Hypertension**	4,315 (4.6)	3,656 (4.4)	465 (8.0)	194 (3.9)	<0.001
- **Ischemic heart disease**	444 (0.5)	316 (0.4)	101 (1.7)	27 (0.5)	<0.001
- **Cardiac dysrhythmias**	357 (0.4)	270 (0.3)	74 (1.3)	13 (0.3)	<0.001
- **Heart failure**	206 (0.2)	121 (0.1)	76 (1.3)	9 (0.2)	<0.001
Digestive diseases	3,841 (4.1)	3,163 (3.8)	391 (6.7)	287 (5.8)	<0.001
- **Peptic ulcer**	120 (0.1)	95 (0.1)	15 (0.3)	10 (0.2)	0.004
- **Chronic liver disease**	3,516 (3.7)	2,916 (3.5)	345 (5.9)	255 (5.2)	<0.001
- **Liver failure, cirrhosis or cirrhotic complications**	17 (0.02)	15 (0.02)	2 (0.03)	0 (0)	0.451
- **Biliary disease**	105 (0.1)	79 (0.1)	14 (0.2)	12 (0.2)	<0.001
- **Gastrointestinal hemorrhage**	181 (0.2)	141 (0.2)	27 (0.5)	13 (0.3)	<0.001
Diabetes mellitus	12,331 (13.1)	8,827 (10.6)	2,181 (37.6)	1,323 (26.9)	<0.001
Malignant tumors	770 (0.8)	495 (0.6)	175 (3.0)	100 (2.0)	<0.001
Nervous system diseases	331 (0.4)	249 (0.3)	64 (1.1)	18 (0.4)	<0.001
- **Cerebrovascular events**	314 (0.3)	239 (0.3)	59 (1.0)	16 (0.3)	<0.001
- **Other nervous system diseases** †	17 (0.02)	10 (0.01)	5 (0.09)	2 (0.04)	0.001
Respiratory diseases ‡	128 (0.1)	80 (0.1)	36 (0.6)	12 (0.2)	<0.001
Kidney diseases	373 (0.4)	256 (0.3)	103 (1.8)	14 (0.3)	<0.001
HIV infection	14 (0.01)	13 (0.02)	0 (0)	1 (0.02)	0.638
Days from the start of designated clinic	24.8 ± 10.6	23.6 ± 10.6	32.7 ± 5.1	35.7 ± 4.2	<0.001
Age- and sex-specified complete vaccination rate (%)	54.2 ± 22.3	56.1 ± 22.2	36.2 ± 16.6	42.7 ± 15.7	<0.001

Number of hospitalizations in the past year (n, %)					<0.001
- **0**	91,667 (97.6)	81,424 (97.9)	5,465 (94.1)	4,778 (97.1)	
- **1**	1,850 (2.0)	1,435 (1.7)	296 (5.1)	119 (2.4)	
- **≥2**	366 (0.4)	295 (0.4)	47 (0.8)	24 (0.5)	
Body mass index (kg/m^2)	24.4 ± 4.7	24.5 ± 4.7	23.9 ± 4.4	24.0 ± 4.2	<0.001
Missing (%)	81.9	83.4	65.4	76.0	
Hemoglobin A_{1c}	6.4 ± 1.0	6.3 ± 1.0	6.5 ± 1.1	6.4 ± 1.0	<0.001
Missing (%)	72.4	76.6	31.3	49.2	
Follow-up duration (days)	30 (30-30)	30 (30-30)	30 (30-30)	30 (29-30)	<0.001

All co-morbidities were represented as binary parameters.

Categorical variables were presented as number (percentage). Follow-up duration was expressed in median (25th percentile - 75th percentile). Age was expressed in mean ± standard deviation. Qualitative and quantitative differences between subgroups were analyzed by Chi-square or Fisher's exact tests for categorical parameters and Student's *t* test or Mann-Whitney *U* test for continuous parameters, as appropriate. All patients had available information on clinical characteristics in Table 1.

† Other nervous system disease was defined by ICD-9-CM diagnosis codes for inflammatory diseases of the central nervous system (ICD-9-CM codes: 320-327), hereditary and degenerative diseases of the central nervous system (ICD-9-CM codes: 330-337), and other disorders of the central nervous system (ICD-9-CM codes: 340-345).

‡ Respiratory system disease was defined by ICD-9-CM diagnosis codes chronic obstructive pulmonary disease and allied conditions (ICD-9-CM codes: 490-496), pneumoconioses and other lung diseases due to external agents (ICD-9-CM codes: 500-508) in previous 3 months, and other diseases of respiratory system (ICD-9-CM codes: 510-519) in previous 3 months.

HIV = human immunodeficiency virus.

Table 2. Baseline clinical characteristics and balancing diagnositcs before and after propensity score weighting between COVID-19 patients who did not use oral antiviral agents, used molnupiravir, or used nirmatrelvir/ritonavir.

	Before propensity score weighting					After propensity score weighting				
Clinical characteristics	**COVID-19 oral antiviral non-user N=83,154**	**Use of molnupiravir N=5,808**	**Use of nirmatrelvir/ ritonavir N=4,921**	**ASMD[@]**	**ASMD^**	**COVID-19 oral antiviral non-user N=4,758**	**Use of molnupiravir N=4,798**	**Use of nirmatrelvir/ ritonavir N=4,921**	**ASMD[@]**	**ASMD^**
Age (years)	46.1 ± 20.8	75.4 ± 12.1	70.8 ± 12.1	2.044	0.377	70.5 ± 12.2	71.1 ± 11.7	70.8 ± 12.1	0.024	0.023
Male sex (n, %)	36,706 (44.1)	2,703 (46.5)	2,247 (45.7)	0.031	0.018	2,178 (45.8)	2,246 (46.8)	2,247 (45.7)	0.002	0.023
Comorbidities (n, %)										
Cardiovascular diseases	3,852 (4.6)	544 (9.4)	216 (4.4)	0.012	0.243	216 (4.5)	220 (4.6)	216 (4.4)	0.007	0.009
Digestive diseases	3,163 (3.8)	391 (6.7)	287 (5.8)	0.087	0.038	276 (5.8)	296 (6.2)	287 (5.8)	0.001	0.014
Diabetes mellitus	8,827 (10.6)	2,181 (37.6)	1,323 (26.9)	0.367	0.241	1,283 (27.0)	1,325 (27.6)	1,323 (26.9)	0.002	0.017
Malignant tumor	495 (0.6)	175 (3.0)	100 (2.0)	0.102	0.070	89 (1.9)	104 (2.2)	100 (2.0)	0.011	0.010
Nervous system diseases	249 (0.3)	64 (1.1)	18 (0.4)	0.011	0.122	18 (0.4)	21 (0.4)	18 (0.4)	0.002	0.013
Respiratory diseases	80 (0.1)	36 (0.6)	12 (0.2)	0.030	0.076	11 (0.2)	14 (0.3)	12 (0.2)	0.001	0.008
Kidney diseases	256 (0.3)	103 (1.8)	14 (0.3)	0.004	0.280	14 (0.3)	17 (0.4)	14 (0.3)	0.004	0.013
Days from the start of designated clinic	23.6 ± 10.6	32.7 ± 5.1	35.7 ± 4.2	2.879	0.713	35.6 ± 4.3	35.6 ± 4.2	35.7 ± 4.2	0.024	0.006
Age- and sex-specified complete vaccination rate (%)	55.9 ± 22.2	36.1 ± 16.7	42.6 ± 15.8	0.847	0.413	42.8 ± 15.7	42.5 ± 15.7	42.6 ± 15.8	0.014	0.007
Number of hospitalizations in the past year (n, %)										
- 0	81,424 (97.9)	5,465 (94.1)	4,778 (97.1)			4,618 (97.1)	4,646 (96.8)	4,778 (97.1)		
- 1	1,435 (1.7)	296 (5.1)	119 (2.4)	0.045	0.174	117 (2.5)	123 (2.6)	119 (2.4)	0.003	0.009
- ≥2	295 (0.4)	47 (0.8)	24 (0.5)	0.019	0.046	23 (0.5)	29 (0.6)	24 (0.5)	0.001	0.015

Use of COVID-19 oral antiviral referred to the use of molnupiravir or nirmatrelvir/ritonavir at baseline or during follow-up. 99.3% of the COVID-19 oral antiviral users used the antiviral drugs within the first 2 days of follow-up.
An ASMD <0.1 indicated good balance between COVID-19 oral antiviral users and non-users. Parameters with ASMD ≥0.1 would be adjusted in doubly robust model.
The effective sample size after propensity score weighting was 8,079, 3,399, and 4,921 in non-users, molnupiravir users, and nirmatrelvir/ritonavir users respectively.
[@] ASMD between COVID-19 oral antiviral non-users and users of nirmatrelvir/ritonavir.
^ ASMD between users of molnupiravir and users of nirmatrelvir/ritonavir.
ASMD = absolute standardized mean difference, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 3. Weighted Cox proportional hazard regression after propensity score weighting on association between use of COVID-19 oral antiviral drugs with the development of primary and secondary endpoints in all COVID-19 patients who attended designated clinic in Hong Kong, and the subgroup of patients aged 60 years or above or aged below 60 years with comorbidities.

All COVID-19 patients

COVID-19 oral antiviral use	Hospital admission		Death/ICU admission/Use of invasive mechanical ventilation	
	Weighted HR (95% CI)	***P* value**	**Weighted HR (95% CI)**	***P* value**
No oral antiviral use	Referent		Referent	
Use of molnupiravir	1.17 (0.99 – 1.39)	0.062	1.12 (0.68 – 1.82)	0.663
Use of nirmatrelvir/ritonavir	0.79 (0.65 – 0.95)	0.011	0.81 (0.47 – 1.39)	0.448
No oral antiviral use	0.85 (0.72 – 1.01)	0.062	0.90 (0.55 – 1.47)	0.663
Use of molnupiravir	Referent		Referent	
Use of nirmatrelvir/ritonavir	0.67 (0.55 – 0.81)	<0.001	0.73 (0.41 – 1.27)	0.265

All COVID-19 patients aged 60 years or above or aged below 60 years with comorbidities

COVID-19 oral antiviral use	Hospital admission		Death/ICU admission/Use of invasive mechanical ventilation	
	Weighted HR (95% CI)	***P* value**	**Weighted HR (95% CI)**	***P* value**
No oral antiviral use	Referent		Referent	
Use of molnupiravir	1.07 (0.90 - 1.26)	0.472	1.04 (0.63 - 1.73)	0.874
Use of nirmatrelvir/ritonavir	0.76 (0.63 - 0.92)	0.004	0.81 (0.47 - 1.39)	0.447
No oral antiviral use	0.94 (0.79 - 1.11)	0.472	0.96 (0.58 - 1.59)	0.874
Use of molnupiravir	Referent		Referent	
Use of nirmatrelvir/ritonavir	0.72 (0.59 - 0.87)	0.001	0.78 (0.44 - 1.38)	0.392

CI = confidence interval, HR = hazard ratio, ICU = intensive care unit.

FIGURE LEGENDS

Figure 1. Cumulative incidence of A. hospital admission and B. admission to intensive care unit (ICU)/ use of invasive mechanical ventilation (IMV)/ death in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection / COVID-19 who did not receive oral antiviral agents, received molnupiravir, or received nirmatrelvir/ritonavir after propensity score (PS) weighting.

Figure 2. Cumulative incidence of A. hospital admission and B. admission to intensive care unit (ICU)/ use of invasive mechanical ventilation (IMV)/ death in the subgroup of patients aged 60 years or above or aged below 60 years with comorbidities who did not receive oral antiviral agents, received molnupiravir, or received nirmatrelvir/ritonavir after propensity score (PS) weighting.

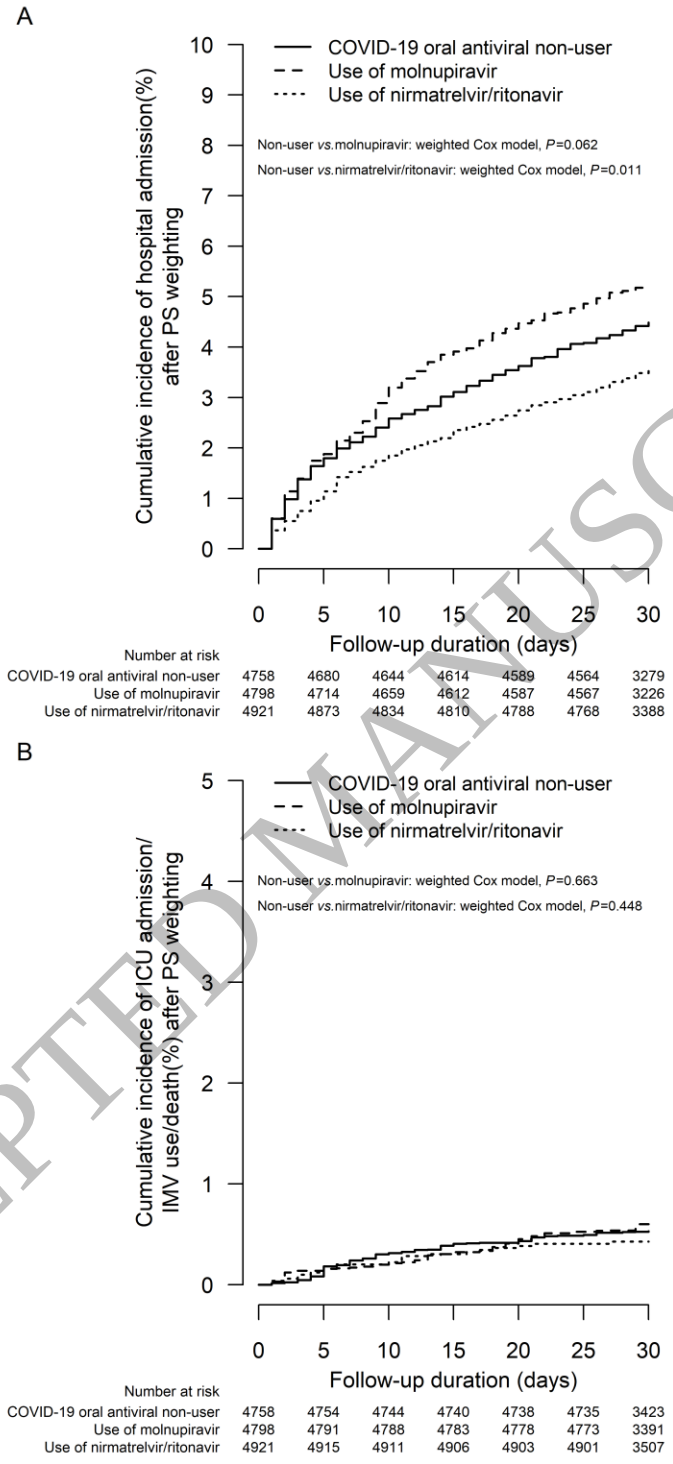

Figure 1
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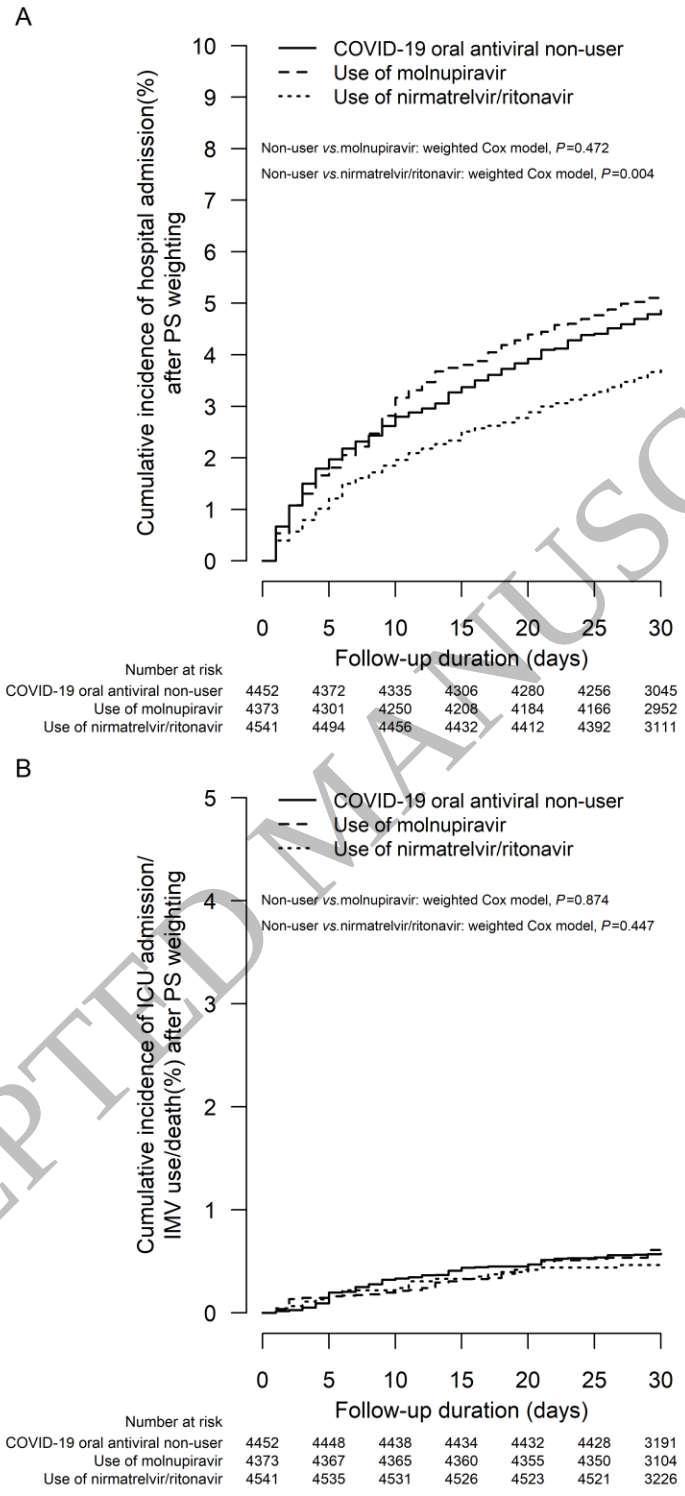

Figure 2
114x229 mm (.31 x DPI)