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Comparative effectiveness of combination therapy with nirmatrelvir-ritonavir and molnupiravir versus monotherapy with molnupiravir or nirmatrelvir-ritonavir in hospitalized COVID-19 patients: A target trial emulation study

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ABSTRACT

Background: Molnupiravir and nirmatrelvir-ritonavir have demonstrated efficacy in reducing hospitalization and mortality among unvaccinated, high-risk COVID-19 outpatients. However, their impact on hospitalized adults remains unclear. Preclinical studies suggest that combining these antivirals may reduce viral shedding and enhance survival.

Methods: This target trial emulation study compared the safety and efficacy of combined molnupiravir and nirmatrelvir-ritonavir versus monotherapy in hospitalized COVID-19 patients in Hong Kong. Data from 28,355 patients aged 18 and older, treated within five days of hospital admission between March 16, 2022, and March 31, 2024, were analyzed. Inverse probability of treatment weighting (IPTW) was used to balance baseline characteristics and outcomes, including mortality, ICU admission, and ventilatory support, which were analyzed using Cox proportional hazards models.

Results: Nirmatrelvir-ritonavir monotherapy significantly reduced mortality risk (HR: 0.62; 95% CI 0.50-0.77; ARR: -3.16%) compared to combination therapy, with no differences in ICU admission or ventilatory support. It also lowered risks of acute liver injury (HR: 0.53 [95% CI 0.32-0.88]), kidney injury (HR: 0.61 [95% CI 0.51-0.74]), and hyperglycaemia (HR: 0.73 [95% CI 0.57-0.93]).

Conclusion: Combining nirmatrelvir-ritonavir and molnupiravir does not significantly reduce mortality, ICU admissions, or ventilatory support needs in hospitalized COVID-19 adults. Nirmatrelvir-ritonavir monotherapy is more effective, but further randomized controlled trials are required to confirm these findings.

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Introduction

Since May 2022, molnupiravir and nirmatrelvir-ritonavir have become the primary oral antiviral treatments in Hong Kong for combating the ongoing COVID-19 pandemic. This period, marked by the fifth wave of the pandemic, has tragically claimed over 13,100 lives, with individuals aged 70 years and older representing 87% of these fatalities [1]. While randomized controlled trials [2–4] have underscored the effectiveness of both nirmatrelvir-ritonavir and molnupiravir in reducing the incidence of hospitalization and mortality, a lack of evidence regarding their utilization in hospitalized settings persists.

Current international treatment guidelines [5–7] do not provide specific recommendations for using oral antiviral therapy, including combination therapy, in hospitalized COVID-19 adults. A recent study in Hong Kong demonstrated that nirmatrelvir-ritonavir and molnupiravir can reduce overall mortality among hospitalized patients, irrespective of their vaccination status [8]. Nevertheless, more comprehensive real-world data are needed to evaluate the safety and efficacy of a combined nirmatrelvir-ritonavir and molnupiravir regimen in high-risk hospitalized settings during the Omicron era [9–11].

The objective of this study is to evaluate the clinical efficacy of molnupiravir, nirmatrelvir-ritonavir, and their potential combined effects among hospitalized COVID-19 adults in Hong Kong during the SARS-CoV-2 Omicron subvariant pandemic wave from March 16, 2022, to March 31, 2024.

Nirmatrelvir-ritonavir inhibits the SARS-CoV-2 main protease, while molnupiravir induces lethal mutagenesis. Both agents have demonstrated additive or synergistic antiviral effects, delaying the emergence of resistance in preclinical models [12–14]. In clinical practice, a small subset of high-risk inpatients, such as those of advanced age with multiple comorbidities, immunocompromised, have received dual oral therapy at the clinician's discretion, typically as salvage or escalation therapy when rapid viral control was prioritized, remdesivir access or timing was constrained, or the viral replication phase was suspected to be prolonged early in admission [15].

Although current guidelines do not endorse combination oral antiviral therapy and are not supported by randomized controlled trial data for hospitalized patients, real-world use has been reported in select cases, particularly among immunocompromised individuals with persistent infection. The RECOVERY trial found no significant improvement in clinical outcomes with the addition of molnupiravir or nirmatrelvir-ritonavir to usual care in hospitalized patients. However, low recruitment limited the ability to exclude a clinically meaningful benefit, especially for nirmatrelvir-ritonavir. Observational studies and case reports suggest that combination therapy may be well-tolerated and potentially beneficial in cases that are difficult to treat, but further research is needed to define its role. This low-frequency practice within centralized health systems reflects the need for individualized decision-making in complex clinical scenarios but underscores the importance of ongoing evaluation and evidence generation for dual oral antiviral strategies in COVID-19 management.

In this target emulation trial, we employ real-world data from electronic health records, matching based on inverse probability of treatment weighting (IPTW), and statistical methods to simulate a target trial assessing the effects of nirmatrelvir-ritonavir and molnupiravir on hospitalized COVID-19 adults in Hong Kong. Through generating evidence on the comparative effectiveness of these therapeutic strategies, we aim to enhance the management of hospitalized COVID-19 adults and address the gap in existing clinical practice guidelines.

Methods

Data sources

The clinical data, including demographic characteristics, diagnoses, prescriptions, and laboratory test results, originated from the electronic health records collected by the Hospital Authority (HA). HA manages all public inpatient and outpatient services, maintaining the comprehensive electronic health records database and providing real-time updated clinical data for routine practice across all clinics and hospitals. The Centre for Health Protection (CHP) of the Government of the Hong Kong Special Administrative Region (HKSAR) provided a comprehensive database of COVID-19 cases as well, given that all individuals in Hong Kong were required to report positive results of the polymerase chain reaction and rapid antigen tests on a mandatory (before December 29, 2022) and voluntary (starting from December 29, 2022 [16]) basis to CHP. Meanwhile, death records were sourced from the Hong Kong Deaths Registry, and the Department of Health (DH) provided the vaccination records. These databases were linked using anonymized unique patient identifiers and have been widely used in previous studies evaluating the efficacy of COVID-19 drugs and the effectiveness of vaccination strategies [17–19]. ICU admission and ventilatory support were identified from the Hospital Authority's standardized electronic order sets and procedure/device logs (Clinical Management System), using harmonized codes and definitions applied across all public hospitals (Supplement Table 2).

Study design and eligibility criteria

This is a target trial emulation study aiming to compare the effectiveness of combination use of nirmatrelvir-ritonavir and molnupiravir, molnupiravir monotherapy, and nirmatrelvir-ritonavir monotherapy among hospitalized COVID-19 patients. Details of the target trial emulation study were presented in Supplement Table 1. COVID-19 cases included in this study were confirmed by positive records of RT-PCR and RAT from 16 March 2022 (when nirmatrelvir-ritonavir became available in Hong Kong) to 31 March 2024. The inclusion criteria included: 1) Patients aged $\geq$ 18 years; 2) hospitalized patients; 3) received either combination treatment with nirmatrelvir-ritonavir and molnupiravir or molnupiravir monotherapy or nirmatrelvir-ritonavir monotherapy within 5 days of hospital admission.

The index date was defined as the date of prescription for nirmatrelvir-ritonavir or molnupiravir, and all medications were provided on or after the date of hospital admission. The combination treatment must be issued on the same day. The details of doses, delivery route and schedule were included in Supplement Table 1. Subjects who 1) initiated nirmatrelvir-ritonavir or molnupiravir over 5 days after COVID-19 diagnosis; 2) had contraindications to nirmatrelvir-ritonavir or molnupiravir, including severe liver impairment (cirrhosis, hepatocellular carcinoma, or liver transplant) or severe renal impairment (estimated glomerular filtration rate $<$30 mL/min/1.73m^2, dialysis, or renal transplant), used interacting drugs (such as amiodarone, or direct oral anticoagulants) within 90 days before the index date 3); used immunomodulatory agents (such as Tocilizumab, Baricitinib, and Interferon beta-1b) within 90 days before the index date and 4) had missing data of lymphocyte count at baseline were excluded. Patients were followed from the index date until the earliest occurrence of the outcome, death, 90 days after the index date, or the end of data availability (30 April 2024).

Outcomes

The primary outcome was all-cause mortality. The secondary outcomes were admission to the ICU or ventilatory support, assessed combined and separately. The occurrence of adverse events, including myocardial infarction, ischaemic stroke, acute liver injury, acute kidney injury, anaemia, rash, hypoglycaemia, hyperglycaemia, gastrointestinal symptoms, and deranged clotting profile within 90 days after the index date, was also explored in our study. The International Classification of Diseases, Ninth Edition (ICD-9-CM), the International Classification of Primary Care-2 (ICPC-2) and the laboratory results were used to identify these adverse events. Definitions for each event were based on clinical parameters or diagnostic codes (ICD-9-CM and ICPC-2) as described in Supplement Table 2. Meanwhile, laboratory results of lymphocyte count at day 0, 5, 14, and 21 during the follow-up period were compared.

Statistical analysis

To address the confounding imbalances between the three treatment groups, we employed an IPTW approach to compare the effect of the treatment strategy. The IPTW-weight was calculated by multinomial logistic regression, adjusting age, sex, Charlson comorbidity index (CCI), number of COVID-19 vaccine doses received, comorbidities (cancer, respiratory disease, diabetes, myocardial infarction, ischaemic stroke, hypertension), and drug use (renin-angiotensin-system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, oral antidiabetic drugs, antiplatelets, immuno-suppressants, corticosteroids, proton pump inhibitors, histamine H2 receptor antagonists, remdesivir) within the past 90 days, ICU admission and ventilatory support within 5 days before treatment at baseline, severity of COVID-19, the time from diagnosis to treatment initiation, and the lymphocyte count at baseline. Based on the World Health Organization's clinical progression scale [20], the severity of COVID-19 infection was evaluated and categorized as the first level (hospitalised patients with no oxygen therapy), the second level (hospitalised patients with oxygen by mask, nasal prongs, non-invasive ventilation, or high flow) and the third level (hospitalised patients with intubation and mechanical ventilation, vasopressors, dialysis, or extracorporeal membrane oxygenation. These confounders were selected according to the literature review of previous studies [21,22] and the suggestions from clinicians specializing in infectious diseases.

An inspection of the standardized mean difference (SMD) between groups in the weighted sample was conducted to assess the balance of covariates and variables, with an SMD of less than 0.1 considered acceptable. Incidence rates were reported with 95% confidence intervals (CIs) estimated based on the Poisson distribution. Absolute risk reduction (ARR) was reported as the difference in cumulative incidence between different therapies. IPTW-weighted Cox proportional hazards regression was used to compare the hazards of outcomes between groups. Hazard ratios (HRs) and their corresponding 95% CIs were reported. The model satisfied the proportional hazards assumption, as determined by the Schoenfeld residual test. For the analysis of each outcome, patients who had experienced prior occurrences of the outcome before the index date were removed from the analysis. To quantify the effect of different treatment strategies on lymphocyte count, the results obtained during hospitalization at days 0, 5, 14, and 21 across treatment groups were compared, and the completion rates of lymphocyte count among hospitalized patients were reported. An imputation approach utilizing the closest record measured 3 days prior to and after each time point to fill the missing values of lymphocyte count was applied. A linear mixed model (LMM) was then built, with individual effects as random effects and adjustments made for the time point of measurement.

Several sensitivity analyses were performed to evaluate the robustness of the primary analysis. Firstly, E-values were computed based on the hazard ratio for each outcome to assess the robustness of the results. The E-value indicates the extent to which the magnitude of association of unmeasured confounders with treatment and outcome is required to disprove the current observed effect. Second, a comparison of the risk of all outcomes in recipients of nirmatrelvir-ritonavir monotherapy versus recipients of molnupiravir monotherapy was conducted. Third, the time interval permitted between COVID-19 diagnosis and initiation of the treatments was reduced from 5 days to 3 days or 1 day. Fourth, for all outcomes apart from mortality, a Fine-Grey competing risk analysis was conducted to adjust for mortality as a competing event. Fifth, the time from admission to treatment initiation was further adjusted in the multinomial logistic regression to generate IPTW weights. Sixth, we applied stabilized IPTW to complete the weighting. Seventh, the lymphocyte count was removed as a covariate in the multinomial logistic regression to generate IPTW weights. Eighth, we additionally included COVID-19 reinfection cases and adjusted the reinfection status of COVID-19 in the multinomial logistic regression to generate IPTW weights. Possible reinfection was defined as the presence of two reported positive tests separated by more than 90 days [23,24].

Subgroup analyses were also conducted to investigate potential interaction effects on the primary outcome. Patients were stratified by age ($<$80, $\geq$80 years), sex (male, female), CCI (0-3, $\geq$4), and number of vaccine doses received (0-1, $\geq$2). Interaction effects between treatment and stratified variables were assessed by the p-values for interaction. Additive interaction effects were also examined, and the relative excess risk due to interaction (RERI) was described.

All statistical tests were two-sided, with a significance level of 0·05. The statistical analyses were conducted using R version 4.0.3 (www.r-project.org). The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklists to ensure transparent reporting.

Results

A total of 28,355 were included in this study (molnupiravir and nirmatrelvir-ritonavir: 1081 molnupiravir: 8416; nirmatrelvir-ritonavir: 18,858). After applying IPTW, a weighted sample comprised 28,389 combination therapy recipients, 28,291 molnupiravir monotherapy recipients, and 28,394 nirmatrelvir-ritonavir monotherapy recipients (Figure 1). The subsequent analyses were primarily based on the weighted sample. All baseline characteristics were well-balanced between the treatment groups with SMD $<$0.1 after weighting (Table 1). The mean (SD) age and the number (proportion) of male were 73.74 (17.01) years and 14,605 (51.4%) for nirmatrelvir-ritonavir and molnupiravir recipients, 74.17 (16.69) years and 14,294 (50.5%) for molnupiravir recipients, and 74.27 (15.06) years and 14,301 (50.4%) for nirmatrelvir-ritonavir recipients.

The 90-day cumulative incidence of all-cause mortality and ICU admission or ventilatory support is shown in Figure 2, and the hazards for each outcome are presented in Table 2. Participants were followed up for a median of 90 days (Interquartile range [IQR]: 90, 90) and documented 6492 (7.63%) cases of death, 866 (1.02%) events of ICU admission, and 1,527 (1.79%) events of ventilatory support. In comparison to subjects received nirmatrelvir-ritonavir in conjunction with molnupiravir, the absolute risk reduction (ARR) was −3.16% (−3.58%, −2.75%) for all-cause mortality, −0.53% (−0.78%, −0.28%) for ICU admission or use of ventilatory support among recipients of nirmatrelvir-ritonavir monotherapy,

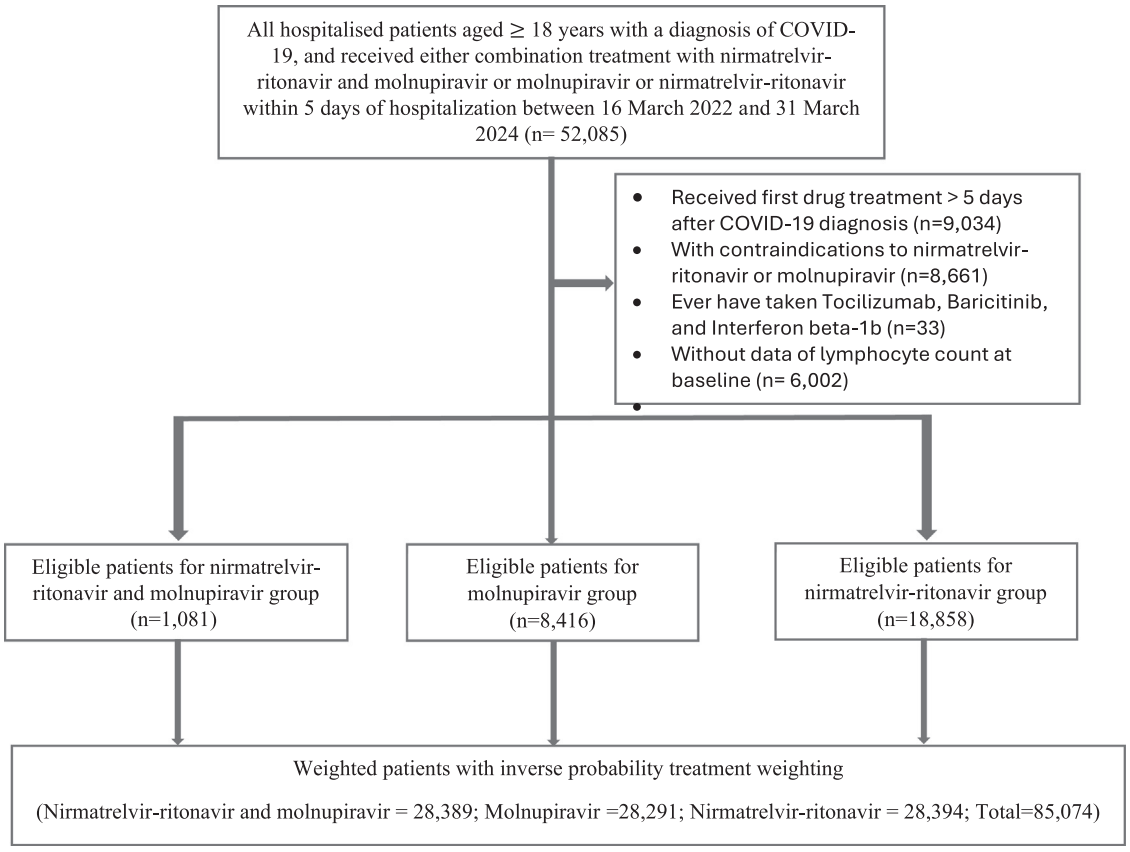

Figure 1. Study flow diagram.
Notes: The patients were weighted by inverse probability of treatment weighting accounted for gender, age, Charlson Comorbidity Index, vaccination status, pre-existing comorbidities, medication use within 90 days, ICU admission and ventilatory support within five days before treatment at baseline, severity of COVID-19 infection, the time from diagnosis to treatment initiation and the lymphocyte count at baseline.

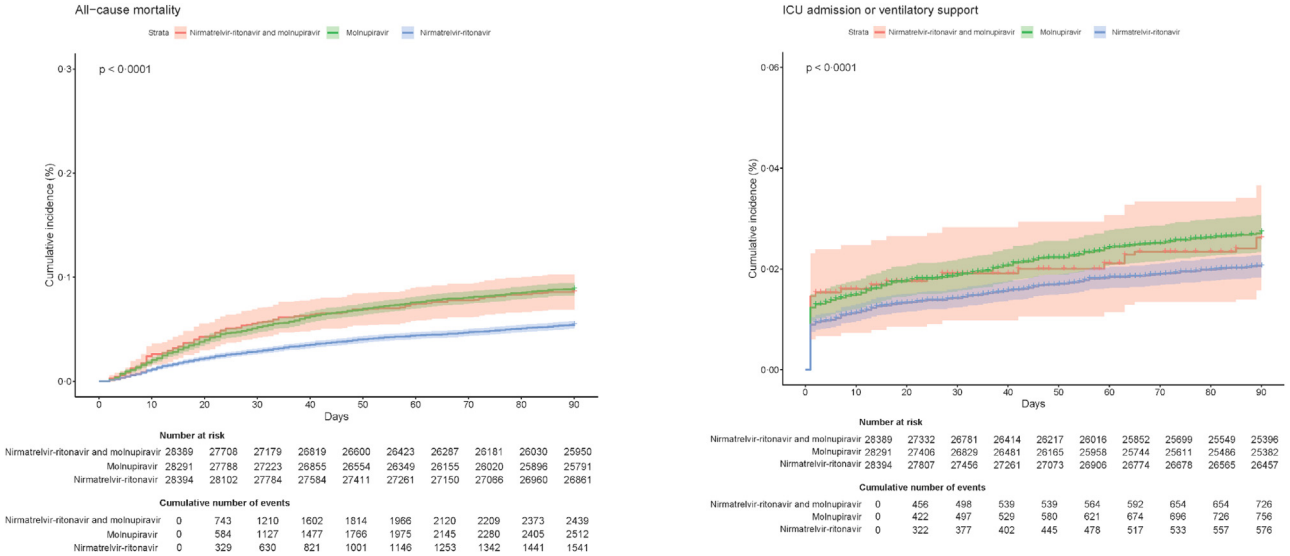

Figure 2. 90-day cumulative incidence of outcomes in recipients of combination treatment with nirmatrelvir-ritonavir and molnupiravir compared to recipients of molnupiravir monotherapy and recipients of nirmatrelvir-ritonavir monotherapy.
ICU = Intensive care unit.
Shared area refers to the 95% confidence interval for the cumulative incidence· The P values indicate the overall P values of the Log-rank test comparing the three treatment groups for each outcome.

Table 1
Baseline characteristics of eligible COVID-19 patients after the inverse probability of treatment weighting (IPTW)

Characteristics	After IPTW Weighting				Before IPTW Weighting			
	Nirmatrelvir-ritonavir and molnupiravir (N = 28,389)	Molnupiravir (N = 28,291)	Nirmatrelvir-ritonavir (N = 28,394)	SMD†	Nirmatrelvir-ritonavir and molnupiravir (N = 1081)	Molnupiravir (N = 8,416)	Nirmatrelvir-ritonavir (N = 18,858)	SMD†
Age, year - mean (SD)	73·74 (17·01)	74·17 (16·69)	74·27 (15·06)	0·022	78·46 (14·38)	75·87 (15·56)	73·36 (15·50)	0·223
Sex, Male (%)	14,605 (51·4)	14,294 (50·5)	14,301 (50·4)	0·014	524 (48·5)	4276 (50·8)	9454 (50·1)	0·031
Charlson Comorbidity Index - mean (SD)	3·87 (2·04)	3·91 (2·14)	3·91 (2·05)	0·013	4·26 (1·86)	4·22 (2·15)	3·75 (2·03)	0·168
COVID-19 vaccination status (%)				0·025				0·185
Unvaccinated	3,952 (13·9)	3,727 (13·2)	3,780 (13·3)		151 (14·0)	1243 (14·8)	2403 (12·7)	
1 dose mRNA	174 (0·6)	153 (0·5)	156 (0·5)		6 (0·6)	64 (0·8)	83 (0·4)	
2 doses mRNA	726 (2·6)	727 (2·6)	733 (2·6)		24 (2·2)	234 (2·8)	477 (2·5)	
≥ 3 doses mRNA	4,674 (16·5)	4,734 (16·7)	4,762 (16·8)		126 (11·7)	1185 (14·1)	3455 (18·3)	
1 dose inactive	717 (2·5)	772 (2·7)	789 (2·8)		35 (3·2)	366 (4·3)	359 (1·9)	
2 doses inactive	2,587 (9·1)	2,675 (9·5)	2,679 (9·4)		129 (11·9)	875 (10·4)	1656 (8·8)	
≥ 3 doses inactive	13,967 (49·2)	13,969 (49·4)	13,945 (49·1)		551 (51·0)	4079 (48·5)	9299 (49·3)	
2 doses mixed	20·7 (0·1)	8·8 (0·0)	9·7 (0·0)		1 (0·1)	4 (0·0)	6 (0·0)	
≥ 3 doses mixed	1,572 (5·5)	1,527 (5·4)	1,540 (5·4)		58 (5·4)	366 (4·3)	1120 (5·9)	
Pre-existing comorbidities (%)								
Cancer	2,918 (10·3)	2,879 (10·2)	2,868 (10·1)	0·004	111 (10·3)	817 (9·7)	1910 (10·1)	0·014
Respiratory disease	2,036 (7·2)	2,102 (7·4)	2,097 (7·4)	0·007	83 (7·7)	697 (8·3)	1319 (7·0)	0·030
Diabetes	8,235 (29·0)	8,229 (29·1)	8,230 (29·0)	0·002	308 (28·5)	2750 (32·7)	5163 (27·4)	0·078
Myocardial infarction	843 (3·0)	849 (3·0)	855 (3·0)	0·002	47 (4·3)	454 (5·4)	341 (1·8)	0·129
Ischaemic stroke	1,610 (5·7)	1,618 (5·7)	1,604 (5·6)	0·002	102 (9·4)	665 (7·9)	830 (4·4)	0·132
Hypertension	14,324 (50·5)	14,398 (50·9)	14,422 (50·8)	0·006	586 (54·2)	4567 (54·3)	9228 (48·9)	0·070
Medication use within 90 days (%)								
Renin-angiotensin-system agents	8,974 (31·6)	8,873 (31·4)	8,889 (31·3)	0·004	349 (32·3)	2993 (35·6)	5512 (29·2)	0·092
Beta blockers	5,662 (19·9)	5,813 (20·5)	5,717 (20·1)	0·010	217 (20·1)	2178 (25·9)	3244 (17·2)	0·141
Calcium channel blockers	11,815 (41·6)	11,656 (41·2)	11,747 (41·4)	0·006	500 (46·3)	3845 (45·7)	7422 (39·4)	0·089
Diuretics	3,063 (10·8)	3,110 (11·0)	3,133 (11·0)	0·005	135 (12·5)	1304 (15·5)	1652 (8·8)	0·137
Nitrates	2,318 (8·2)	2,414 (8·5)	2,396 (8·4)	0·009	94 (8·7)	1046 (12·4)	1238 (6·6)	0·134
Lipid lowering agents	12,400 (43·7)	12,620 (44·6)	12,562 (44·2)	0·012	535 (49·5)	4408 (52·4)	7570 (40·1)	0·166
Insulins	1,892 (6·7)	1,828 (6·5)	1,852 (6·5)	0·005	62 (5·7)	809 (9·6)	973 (5·2)	0·114
Antidiabetic drugs	6,509 (22·9)	6,710 (23·7)	6,683 (23·5)	0·012	237 (21·9)	2263 (26·9)	4153 (22·0)	0·081
Antiplatelets	8,136 (28·7)	8,379 (29·6)	8,316 (29·3)	0·014	390 (36·1)	3251 (38·6)	4611 (24·5)	0·205
Immunosuppressants	615 (2·2)	513 (1·8)	535 (1·9)	0·017	24 (2·2)	257 (3·1)	225 (1·2)	0·087
Corticosteroids	2,114 (7·4)	1,854 (6·6)	1,891 (6·7)	0·023	70 (6·5)	718 (8·5)	1103 (5·8)	0·070
Proton pump inhibitors	8,414 (29·6)	8,529 (30·1)	8,533 (30·1)	0·007	346 (32·0)	3376 (40·1)	4749 (25·2)	0·214
Histamine H2 receptor antagonists	6,586 (23·2)	6,537 (23·1)	6,531 (23·0)	0·003	268 (24·8)	2142 (25·5)	4076 (21·6)	0·060
Remdesivir	277 (1·0)	258 (0·9)	255 (0·9)	0·006	5 (0·5)	94 (1·1)	152 (0·8)	0·049
ICU admission within 5 days before treatment (%)	158 (0·6)	178 (0·6)	179 (0·6)	0·007	12 (1·1)	59 (0·7)	104 (0·6)	0·041
Ventilatory support within 5 days before treatment (%)	74 (0·3)	72 (0·3)	74 (0·3)	0·001	8 (0·7)	30 (0·4)	31 (0·2)	0·059
Clinical progression scale †† (%)				0·025				0·046
Level 1	28,239 (99·5)	28,122 (99·4)	28,219 (99·4)		1074 (99·4)	8340 (99·1)	18,768 (99·5)	
Level 2	33 (0·1)	73 (0·3)	76 (0·3)		2 (0·2)	28 (0·3)	48 (0·3)	
Level 3	117 (0·4)	96 (0·3)	99 (0·3)		5 (0·5)	48 (0·6)	42 (0·2)	
Time from diagnosis to treatment initiation- mean (SD)	0·72 (0·86)	0·75 (0·95)	0·75 (0·96)	0·026	0·72 (0·86)	0·79 (0·99)	0·74 (0·95)	0·040
Lymphocytes count - mean (SD)	1·02 (0·55)	1·08 (2·47)	1·09 (2·69)	0·024	1·03 (0·56)	1·08 (2·68)	1·06 (2·00)	0·017

IPTW, inverse probability of treatment weighting; SMD, Standardised mean difference; SD, Standard deviation; IQR , interquartile range; CCI, Charlson Comorbidity Index; ICU, Intensive care units;.

† SMD<0·1 indicates balance between groups·.

†† Level 1: Hospitalised patients with no oxygen therapy; Level 2: Hospitalised patients with oxygen by mask, nasal prongs, non-invasive ventilation or high flow; Level 3: Hospitalised patients with intubation and mechanical ventilation, vasopressors, dialysis, or extracorporeal membrane oxygenation.

Table 2
Risk of outcomes for COVID-19 patients receiving combined use of molnupiravir and nirmatrelvir ritonavir compared with patients receiving molnupiravir alone and patients receiving nirmatrelvir-ritonavir alone after weighting

Outcome event	Nirmatrelvir-ritonavir and molnupiravir (N = 28,389)			Molnupiravir (N = 28,291)					Nirmatrelvir-ritonavir (N = 28,394)				
	Events	Cumulative incidence (%)	Incidence rate (Per 10,000 Person days)	Events	Cumulative incidence (%)	Incidence rate (Per 10,000 Person days)	ARR (95% CI) (%)	†Adjusted HR (95% CI)	Events	Cumulative incidence (%)	Incidence rate (Per 10,000 Person days)	ARR (95% CI) (%)	†Adjusted HR (95% CI)
All-cause mortality	2,439	8·59	10·15 (9·75, 10·56)	2,512	8·88	10·48 (10·07, 10·89)	0·29 (−0·18, 0·75)	1·03 (0·83-1·28)	1,541	5·43	6·24 (5·93, 6·56)	−3·16 (−3·58, −2·75)	0·62 (0·50-0·77)
ICU admission or ventilatory support	726	2·56	3·07 (2·85, 3·30)	756	2·67	3·20 (2·98, 3·44)	0·11 (−0·15, 0·38)	1·04 (0·68-1·60)	576	2·03	2·36 (2·17, 2·56)	−0·53 (−0·78, −0·28)	0·78 (0·51-1·19)
ICU admission	337	1·19	1·42 (1·27, 1·58)	264	0·93	1·11 (0·98, 1·25)	−0·26 (−0·42, −0·09)	0·78 (0·41-1·50)	266	0·94	1·08 (0·95, 1·22)	−0·25 (−0·42, −0·08)	0·78 (0·42-1·46)
Use of ventilatory support	484	1·70	2·03 (1·85, 2·21)	605	2·14	2·55 (2·35, 2·76)	0·44 (0·21, 0·66)	1·26 (0·75-2·10)	438	1·54	1·79 (1·62, 1·96)	−0·16 (−0·37, 0·05)	0·89 (0·54-1·48)
Myocardial infarction	192	0·71	0·84 (0·72, 0·96)	198	0·74	0·87 (0·75, 1·00)	0·03 (−0·11, 0·17)	1·04 (0·49-2·24)	110	0·41	0·47 (0·39, 0·56)	−0·30 (−0·42, −0·17)	0·57 (0·27-1·21)
Ischaemic stroke	34	0·13	0·15 (0·10, 0·21)	125	0·46	0·55 (0·45, 0·65)	0·33 (0·25, 0·43)	3·66 (0·87-15·47)	90	0·33	0·38 (0·31, 0·47)	0·20 (0·12, 0·29)	2·59 (0·62-10·76)
Acute liver injury	566	2·04	2·43 (2·23, 2·64)	444	1·61	1·92 (1·74, 2·10)	−0·43 (−0·65, −0·21)	0·79 (0·48-1·30)	310	1·11	1·28 (1·14, 1·43)	−0·93 (−1·14, −0·73)	0·53 (0·32-0·88)
Acute kidney injury	3,563	13·77	17·92 (17·34, 18·52)	3,244	12·60	16·23 (15·68, 16·80)	−1·17 (−1·76, −0·59)	0·91 (0·75-1·10)	2,347	8·76	10·72 (10·29, 11·17)	−5·01 (−5·55, −4·47)	0·61 (0·51-0·74)
Anaemia	726	2·76	3·30 (3·06, 3·55)	788	3·01	3·61 (3·36, 3·86)	0·25 (−0·04, 0·53)	1·09 (0·72-1·65)	720	2·68	3·13 (2·91, 3·37)	−0·08 (−0·36, 0·20)	0·96 (0·64-1·43)
Rash	16	0·06	0·07 (0·04, 0·11)	24	0·09	0·10 (0·06, 0·15)	0·03 (−0·01, 0·07)	1·52 (0·18-12·77)	10	0·04	0·04 (0·02, 0·07)	−0·02 (−0·06, 0·01)	0·63 (0·08-5·16)
Hypoglycaemia	52	0·19	0·22 (0·17, 0·29)	93	0·34	0·40 (0·32, 0·49)	0·15 (0·07, 0·24)	1·80 (0·42-7·65)	76	0·27	0·31 (0·24, 0·39)	0·08 (0·00, 0·16)	1·40 (0·33-5·89)
Hyperglycaemia	2,037	8·46	10·74 (10·27, 11·21)	1,633	6·79	8·43 (8·03, 8·85)	−1·67 (−2·14, −1·20)	0·79 (0·61-1·03)	1,542	6·26	7·59 (7·22, 7·98)	−2·20 (−2·66, −1·73)	0·73 (0·57-0·93)
GI symptoms	0	0	0	0	0	0	0	NA	0	0	0	0	NA
Deranged clotting profile	195	0·69	0·82 (0·70, 0·94)	221	0·79	0·93 (0·81, 1·06)	0·10 (−0·04, 0·24)	1·14 (0·57-2·29)	151	0·54	0·62 (0·52, 0·72)	−0·15 (−0·28, −0·03)	0·76 (0·38-1·53)

ICU=Intensive care units; GI: Gastrointestinal; ARR=Absolute risk reduction; HR=Hazard ratio; CI=Confidence interval; NA=Not applicable due to insufficient number of cases· †Hazard ratios were obtained from Cox proportional hazards regression after weighing.

Table 3
The effects of combined use of molnupiravir and nirmatrelvir ritonavir compared with molnupiravir alone and nirmatrelvir-ritonavir alone over the 0-21 days follow-up in linear mixed models.

	Nirmatrelvir-ritonavir and molnupiravir (N = 28,389)	Molnupiravir (N = 28,291)	Nirmatrelvir-ritonavir (N = 28,394)
Lymphocyte count[§], 10^9/L			
Mean at day 0	1·02 (1·01, 1·02)	1·08 (1·05, 1·11)	1·09 (1·06, 1·11)
Mean at day 5	1·28 (1·27, 1·29)	1·32 (1·27, 1·37)	1·39 (1·32, 1·45)
Mean at day 14	1·14 (1·12, 1·16)	1·18 (1·16, 1·20)	1·28 (1·08, 1·49)
Mean at day 21	1·19 (1·17, 1·22)	1·13 (1·11, 1·16)	1·22 (1·04, 1·40)
Estimate (95% CI)[*]	Ref	0.02 (−0.23, 0.28)	0.00 (−0.25, 0.25)
P value[*]	Ref	0.8616	0.9902

CI, Confidence interval;.
[§] An imputation approach utilising the closest record measured three days prior and post each time point to fill the missing values of outcomes at these designated time points was applied·.
[*] The effect estimates and p-value were computed via linear mixed models after weighing, with individual effects as random effects and adjusting the timepoint of measurement.

and 0.29% (−0.18%, 0.75%) for all-cause mortality, 0.11% (−0.15%, 0.38%) for ICU admission or use of ventilatory support among recipients of molnupiravir monotherapy. Compared to the combination therapy, nirmatrelvir-ritonavir monotherapy exhibited a significantly lower risk of mortality (HR [95% CI]: 0.62 [0.50, 0.77]), while molnupiravir monotherapy recorded similar hazards for all primary outcomes. Comparable risks of ICU admission or use of ventilatory support were observed between the three treatment groups.

Regarding the adverse events occurring after initiation of therapy (Table 2), a lower risk of acute liver injury (HR [95% CI]: 0.53 [0.32, 0.88]), acute kidney injury (HR [95% CI]: 0.61 [0.51, 0.74]), and hyperglycaemia (HR [95% CI]: 0.73 [0.57, 0.93]) was documented among patients who received nirmatrelvir-ritonavir, comparing to the recipients of nirmatrelvir-ritonavir and molnupiravir. The cumulative incidence of adverse effects, including ischaemic stroke, anaemia, rash, hypoglycaemia, gastrointestinal symptoms, and deranged clotting profile, was similar among different therapies.

Additionally, Table 3 demonstrated the mean lymphocyte count at day 0, 5, 14, and 21. There was no significant difference in the effect on lymphocyte count between nirmatrelvir-ritonavir monotherapy, molnupiravir monotherapy, and the combined treatment.

The findings on all-cause mortality were similar across all subgroups (Table 4). No significant interaction effects were found in the multiplicative scale (Table 4) or additive scale (Supplement Table 3) for age, sex, CCI, and COVID-19 vaccination status in the comparisons between combination therapy and molnupiravir monotherapy, and between combination therapy and nirmatrelvir-ritonavir monotherapy.

A series of sensitivity analyses were conducted to test the robustness of our findings, based on the HRs of 0.62 for all-cause mortality versus combination therapy, the E-values for nirmatrelvir-ritonavir monotherapy was 2.61, suggesting that unobserved confounding variable with at least a 2.61-fold stronger association with mortality would be needed to explain away the current significant HR (Supplement Table 4). The comparison of results in recipients of nirmatrelvir-ritonavir monotherapy and molnupiravir monotherapy is described in Supplement Table 5, indicating a higher risk of all-cause mortality, ventilatory support, incident myocardial infarction, acute liver injury, acute kidney injury, and a deranged clotting profile associated with molnupiravir monotherapy. The results of the primary analysis remained unchanged in other sensitivity analyses, including reducing the time interval permitted between COVID-19 diagnosis and initiation of the treatments from 5 days to 3 days (Supplement Table 6) or 1 day (Supplement Table 7), applying Fine-Gray competing risk models for all outcomes apart from mortality (Supplement Table 8), additionally adjusting time from admission to treatment initiation in the multinomial logistic regression to generate IPTW-weight (Supplement Table 9), applying stabilized IPTW (Supplement Table 10), removing lymphocyte count as a covariate in the multinomial logistic regression to generate IPTW-weight (Supplement Table 11), and including reinfection COVID-19 cases (Supplement Table 12). The completion rate of lymphocyte count among the hospitalized patients was reported in Supplement Table 13.

Discussion

To our knowledge, this is the first real-world study to evaluate the combined effects of molnupiravir and nirmatrelvir-ritonavir and compare their efficacy to that of each antiviral agent used individually in hospitalized COVID-19 adults. Compared with combination therapy, nirmatrelvir-ritonavir monotherapy was associated with significantly lower all-cause mortality, whereas molnupiravir monotherapy showed no significant difference in mortality compared with combination therapy. These findings align with various real-world studies [25–27], suggesting that early initiation of nirmatrelvir-ritonavir during the first 5 days of SARS-CoV-2 infection substantially reduces the risk of progression to severe COVID-19 or death, irrespective of vaccination status, during the Omicron era.

Although combination therapy is not the standard of care and is not endorsed by international guidelines, its limited use occurred in Hong Kong under clinician discretion for selected high-risk inpatients early in their admission, motivated by mechanistic complementarity, preclinical synergy, and pragmatic constraints (e.g., timing or contraindications to remdesivir). Our findings do not demonstrate a mortality or escalation-of-care advantage for routine dual oral therapy in hospitalized adults.

Nonetheless, Real-world evidence evaluating the efficacy of molnupiravir or nirmatrelvir-ritonavir in hospitalized patients has yielded inconsistent results. A Hong Kong study reported significant clinical benefits in terms of disease progression, the necessity for oxygen support, and time to achieve a low viral burden when initiating molnupiravir or nirmatrelvir-ritonavir treatment early in hospitalized patients who did not require oxygen therapy upon admission [28]. Our findings suggest that mortality benefits were more pronounced in patients receiving nirmatrelvir-ritonavir monotherapy, with consistent advantages observed across various SARS-CoV-2 vaccination statuses, admission criteria, respiratory support modalities, and comorbidities.

Table 4
Risk of all-cause mortality in recipients of combination treatment with nirmatrelvir-ritonavir and molnupiravir compared to recipients of molnupiravir monotherapy and recipients of nirmatrelvir-ritonavir monotherapy

Subgroups	Nirmatrelvir-ritonavir and molnupiravir (N = 28,389)			Molnupiravir (N = 28,291)					Nirmatrelvir-ritonavir (N = 28,394)					
	Events	Cumulative incidence (%)	Incidence rate (per 10,000-person days)	Events	Cumulative incidence (%)	Incidence rate (per 10,000-person days)	ARR (95% CI) (%)	†Adjusted HR (95% CI)	p-value for interaction	Events	Cumulative incidence (%)	Incidence rate (per 10,000-person days)	ARR (95% CI) (%)	†Adjusted HR (95% CI)	p-value for interaction
All-cause mortality															
Age									0·4481						0·6443
<80 years	648	3·98	4·55 (4·20, 4·91)	752	4·71	5·39 (5·01, 5·78)	0·72 (0·28, 1·17)	1·18 (0·73-1·92)		463	2·76	3·12 (2·84, 3·41)	−1·22 (−1·61, −0·83)	0·69 (0·42-1·11)	
≥80 years	1,791	14·78	18·30 (17·46, 19·16)	1,760	14·28	17·55 (16·73, 18·38)	−0·50 (−1·38, 0·38)	0·96 (0·76-1·22)		1,078	9·27	10·95 (10·30, 11·62)	−5·51 (−6·33, −4·69)	0·61 (0·48-0·77)	
Sex									0·1901						0·7510
Male	1,459	9·99	11·91 (11·31, 12·54)	1,310	9·17	10·83 (10·25, 11·43)	−0·82 (−1·50, −0·15)	0·91 (0·67-1·23)		882	6·16	7·13 (6·66, 7·61)	−3·82 (−4·45, −3·20)	0·60 (0·45-0·81)	
Female	980	7·11	8·32 (7·80, 8·85)	1,202	8·58	10·12 (9·55, 10·70)	1·47 (0·84, 2·10)	1·21 (0·89-1·65)		660	4·68	5·35 (4·95, 5·77)	−2·43 (−2·98, −1·88)	0·65 (0·48-0·88)	
CCI									0·6794						0·9278
0-3	218	2·04	2·29 (1·99, 2·61)	262	2·47	2·79 (2·46, 3·14)	0·44 (0·04, 0·83)	1·22 (0·51-2·88)		144	1·32	1·48 (1·24, 1·73)	−0·72 (−1·06, −0·38)	0·64 (0·27-1·52)	
≥4	2,222	12·56	15·29 (14·66, 15·94)	2,250	12·71	15·41 (14·78, 16·06)	0·15 (−0·54, 0·84)	1·01 (0·81-1·26)		1,397	8·01	9·37 (8·88, 9·87)	−4·55 (−5·18, −3·92)	0·62 (0·50-0·77)	
COVID-19 vaccination status							0·2844								0.9899
0-1 dose	671	13·86	16·80 (15·55, 18·12)	782	16·81	21·09 (19·62, 22·60)	2·95 (1·50, 4·40)	1·25 (0·85-1·83)		414	8·77	10·30 (9·33, 11·33)	−5·09 (−6·36, −3·83)	0·62 (0·42-0·91)	
≥2 doses	1,768	7·51	8·82 (8·41, 9·24)	1,730	7·32	8·53 (8·13, 8·94)	−0·19 (−0·67, 0·28)	0·97 (0·74-1·26)		1,127	4·76	5·45 (5·14, 5·78)	−2·75 (−3·18, −2·32)	0·62 (0·48-0·80)	

HR, Hazard ratio; CI, Confidence interval; CCI, Charlson Comorbidity Index; ICU, Intensive care units·
† Hazard ratios were obtained from Cox proportional hazards regression after weighing.

Due to their mode of action, antiviral nucleoside analogues like molnupiravir are expected to be most effective when administered immediately before SARS-CoV-2 exposure and during active viral replication (typically within 4-7 days), which often occurs before COVID-19 symptoms manifest [29]. This suggests that the primary outpatient utility of an antiviral nucleoside analogue such as molnupiravir lies in home and institutional settings where community spread of the virus is initially detected. Consequently, molnupiravir may not confer substantial clinical benefits for hospitalized patients who have progressed beyond the viral replication phase, as our investigation shows. These results also concur with the MOVe-IN study conducted during the Alpha wave [30], which reported no substantial decrease in all-cause mortality among hospitalized COVID-19 adults treated with molnupiravir.

Antiviral combination regimens may hold potential therapeutic value in immunocompromised hosts with SARS-CoV-2 infection [15], although our current understanding of their efficacy remains limited. While preclinical data have indicated that such regimens can amplify antiviral potency and mitigate the development of drug-resistant variants [14,31,32], our study did not reveal a significant reduction in mortality compared to nirmatrelvir-ritonavir monotherapy. Several factors could elucidate the disparity between positive outcomes in animal models and clinical results.

The reduced mortality benefit observed with molnupiravir, compared to nirmatrelvir-ritonavir monotherapy, may be attributed to the depletion of B lymphocytes induced by molnupiravir, leading to immunomodulation or immunosuppression. Molnupiravir, a nucleoside analogue antiviral, exerts its effects by inducing lethal mutagenesis through genome error catastrophe. Recent in vitro studies have shown that molnupiravir's active metabolite, β-D-N4-hydroxycytidine (NHC or EIDD-1931), promotes mutagenesis upon interaction with uridine-cytidine kinase 2 (Uck2) [33]. Uck2, a key enzyme in the pyrimidine salvage pathway, converts uridine and cytidine into uridine monophosphate (UMP) and cytidine monophosphate (CMP) and is highly expressed in human B lymphocytes, which are crucial for mounting an immune response to SARS-CoV-2. Although our study did not show significant differences in lymphocyte count between treatment groups, patients receiving molnupiravir monotherapy had the lowest lymphocyte count by day 21. This finding aligns with real-world data, showing a significant reduction in lymphocyte counts in adults with mild-to-moderate COVID-19 treated with molnupiravir [34]. The risk of B lymphocyte depletion appears to be related to the drug's maximum observed concentration (Cmax) and monocyte-lymphocyte uptake [35]. Preclinical studies in dogs have also demonstrated severe decreases in bone marrow cellularity in the femur and sternum at NHC exposures that are lower than the mean clinical exposure at the recommended human dose [36]. These findings highlight the need for further investigation to confirm the immunosuppressive potential of molnupiravir and to elucidate its underlying mechanisms.

Different variants may exhibit unique severity profiles, and the antiviral effects demonstrated in one variant may not apply to others. The study was conducted when the Omicron variant was the dominant Variant of Concern (VOC), while the Rhesus macaque model tested antiviral activities against the Delta VOC [14]. This difference could also elucidate the lack of a mortality benefit in combination treatments compared to nirmatrelvir-ritonavir monotherapy.

Our study revealed a noteworthy association between combination therapy and an increased risk of acute liver and kidney injury. It is essential to note that, although this effect is transient, no significant mortality was observed, and no treatment discontinuations occurred due to the adverse effects of the combination therapy. Similar adverse events have been documented in previous studies involving patients treated with combinations of nirmatrelvir-ritonavir, remdesivir, molnupiravir, and monoclonal antibodies [37]. The heightened occurrence of these unfavorable events in patients receiving combined treatment, as opposed to those receiving nirmatrelvir-ritonavir alone, may be influenced by various factors, including co-morbidities, disease severity, and concomitant medications.

Our study, involving over 28,000 hospitalized COVID-19 adults, predominantly elderly, multiply vaccinated, and with multiple comorbidities, presents a robust illustration of nirmatrelvir–ritonavir monotherapy's real-world efficacy in inpatient COVID-19 management. Given the study's inpatient setting, drug non-compliance issues were significantly reduced. The target trial emulation approach mitigated common observational study biases, such as immortal time bias and selection bias. Uniform clinical decisions guided by the HA Central Committee on Infectious Diseases and Emergency Response across all public hospitals in Hong Kong minimize practice variation.

This study has several limitations. First, conducted during Hong Kong's Omicron wave, caution is warranted when extrapolating findings to other variants or regions. Second, while the design identifies associations, it does not confirm causality. There was a notable imbalance in patient numbers between the monotherapy and combination therapy groups. Despite the use of IPTW to adjust for group differences, unmeasured confounders and indication bias may remain. Further studies with larger patient cohorts in the combination therapy group are warranted to confirm and extend our findings. Third, the small number of outcome events, particularly adverse events, could introduce sparse data bias. Fourth, with 99.5% of the participants categorized as level 1 at the COVID-19 infection severity, the severity score failed to capture the granularity of disease severity accurately. Fifth, despite extensive covariate adjustment and inverse probability of treatment weighting, residual confounding may persist. The WHO severity tier lacked clinical granularity (e.g., serial oxygen requirements and imaging findings), and direct measures of socioeconomic status (SES) were unavailable; both could influence presentation and outcomes. Although Hong Kong's centralized public hospital system reduces financial barriers and standardizes access and treatment pathways, SES-related factors can still shape pre-hospital disease course, timeliness of presentation, and post-discharge outcomes, potentially biasing estimates even after IPTW. Sixth, despite centralized guidance and harmonized coding, residual practice variation in ICU admission thresholds and ventilatory support initiation across sites may persist and could influence secondary outcomes.

Our associations appear robust to unmeasured confounding, as suggested by an E-value of 2.61 for the observed hazard ratio of 0.62 in the comparison involving combination therapy; nevertheless, residual bias and limited generalizability cannot be excluded. Confirmation of the efficacy of combination therapy will require large, multinational, randomized controlled trials.

Oral antivirals are valuable therapeutic arsenals against SARS-CoV-2 as vaccine-induced immunity declines. The study provides convincing evidence that nirmatrelvir-ritonavir monotherapy is superior to combination therapy or molnupiravir monotherapy for treating hospitalized COVID-19 adults. However, further research is needed to consolidate these findings and to explore potential long-term effects and patient-specific factors that may influence treatment outcomes.

Conclusion

Our study identified a significant mortality benefit associated with nirmatrelvir-ritonavir monotherapy in comparison to combination therapies involving nirmatrelvir-ritonavir with molnupiravir or molnupiravir alone among hospitalized COVID-19 adults. These findings were consistent across patients with varying SARS-

CoV-2 vaccination statuses. Despite the current lack of endorsement for nirmatrelvir-ritonavir monotherapy in international and local guidelines for hospitalized COVID-19 adults, our finding offers compelling preliminary evidence supporting its consideration, particularly for patients who do not respond optimally to standard treatment. Further randomized controlled trials are warranted to confirm the validity of the current results.

Authors contributors

MHC, EYFW, BW, YX, WMC, ART, ICKW, EWYC, KYY, and IFNH contributed to the conception and design of the study and performed data acquisition. MHC and EYFW performed data analysis and interpretation. MHC and EYFW wrote the first draft of the manuscript. MHC, EYFW, and IFNH accessed the data and verified the underlying data. All authors had access to the study's data. All authors revised the manuscript critically for important intellectual content. IFNH was responsible for the decision to submit the manuscript.

Ethics approval

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

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Data sharing

Data will not be available for others as the data custodians have not given permission. Academic institutions, government departments, or non-governmental organisations in Hong Kong may apply for access to data through the Hospital Authority's data-sharing portal (https://www3.ha.org.hk/data).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MHC, BW, YX, ART, and WMC declare no competing interests. EYFW has received research grants from the Health Bureau of the Government of the Hong Kong SAR, the Hong Kong Research Grants Council of the Government of the Hong Kong SAR, Narcotics Division, Security Bureau of the Government of the Hong Kong SAR, Social Welfare Department, Labour and Welfare Bureau of the Government of the Hong Kong SAR and National Natural Science Foundation of China, outside the submitted work.

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MHC (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108097.

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