Comparison of safety and efficacy between Nirmatrelvir-ritonavir and molnupiravir in the treatment of COVID-19 infection in patients with advanced kidney disease: a retrospective observational study

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Summary

Background Nirmatrelvir-ritonavir is used in patients with coronavirus disease 2019 (COVID-19) with normal or mild renal impairment (eGFR ≥30 ml/min per 1.73 m^2). There is limited data regarding its use in advanced kidney disease (eGFR <30 ml/min per 1.73 m^2). We performed a retrospective territory-wide observational study evaluating the safety and efficacy of nirmatrelvir-ritonavir when compared with molnupiravir in the treatment of patients with COVID-19 with advanced kidney disease.

Methods We adopted target trial emulation using data from a territory-wide electronic health record database on eligible patients aged ≥18 years with advanced kidney disease (history of eGFR <30 ml/min per 1.73 m^2) who were infected with COVID-19 and were prescribed with either molnupiravir or nirmatrelvir-ritonavir within five days of infection during the period from 16 March 2022 to 31 December 2022. A sequence trial approach and 1:4 propensity score matching was applied based on the baseline covariates including age, sex, number of COVID-19 vaccine doses received, Charlson comorbidity index (CCI), hospitalisation, eGFR, renal replacement therapy, comorbidities (cancer, respiratory disease, myocardial infarction, ischaemic stroke, diabetes, 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 H_2 receptor antagonists, monoclonal antibody infusion) within past 90 days. Individuals were followed up from the index date until the earliest outcome occurrence, death, 90 days from index date or the end of data availability. Stratified Cox proportional hazards regression adjusted with baseline covariates was used to compare the risk of outcomes between nirmatrelvir-ritonavir recipients and molnupiravir recipients which include (i) all-cause mortality, (ii) intensive care unit (ICU) admission, (iii) ventilatory support, (iv) hospitalisation, (v) hepatic impairment, (vi) ischaemic stroke, and (vii) myocardial infarction. Subgroup analyses included age (<70; ≥70 years); sex, Charlson comorbidity index (≤5; >5), and number of COVID-19 vaccine doses received (0–1; ≥2 doses).

Findings A total of 4886 patients were included (nirmatrelvir-ritonavir: 1462; molnupiravir: 3424). There were 347 events of all-cause mortality (nirmatrelvir-ritonavir: 74, 5.06%; molnupiravir: 273, 7.97%), 10 events of ICU admission (nirmatrelvir-ritonavir: 4, 0.27%; molnupiravir: 6, 0.18%), 48 events of ventilatory support (nirmatrelvir-ritonavir: 13, 0.89%; molnupiravir: 35, 1.02%), 836 events of hospitalisation (nirmatrelvir-ritonavir: 218, 23.98%;

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molnupiravir: 618, 28.14%), 1 event of hepatic impairment (nirmatrelvir-ritonavir: 0, 0%; molnupiravir: 1, 0.03%), 8 events of ischaemic stroke (nirmatrelvir-ritonavir: 3, 0.22%; molnupiravir: 5, 0.16%) and 9 events of myocardial infarction (nirmatrelvir-ritonavir: 2, 0.15%; molnupiravir: 7, 0.22%). Nirmatrelvir-ritonavir users had lower rates of all-cause mortality (absolute risk reduction (ARR) at 90 days 2.91%, 95% CI: 1.47–4.36%) and hospitalisation (ARR at 90 days 4.16%, 95% CI: 0.81–7.51%) as compared with molnupiravir users. Similar rates of ICU admission (ARR at 90 days –0.09%, 95% CI: –0.4 to 0.2%), ventilatory support (ARR at 90 days 0.13%, 95% CI: –0.45 to 0.72%), hepatic impairment (ARR at 90 days 0.03%, 95% CI: –0.03 to 0.09%), ischaemic stroke (ARR at 90 days –0.06%, 95% CI: –0.35 to 0.22%), and myocardial infarction (ARR at 90 days 0.07%, 95% CI: –0.19 to 0.33%) were found between nirmatrelvir-ritonavir and molnupiravir users. Consistent results were observed in relative risk adjusted with baseline characteristics. Nirmatrelvir-ritonavir was associated with significantly reduced risk of all-cause mortality (HR: 0.624, 95% CI: 0.455–0.857) and hospitalisation (HR: 0.782, 95% CI: 0.64–0.954).

Interpretation Patients with COVID-19 with advanced kidney disease receiving nirmatrelvir-ritonavir had a lower rate of all-cause mortality and hospital admission when compared with molnupiravir. Other adverse clinical outcomes were similar in both treatment groups.

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Keywords: SARS-CoV-2; Advanced kidney disease; Renal failure; CKD; Molnupiravir; Nirmatrelvir-ritonavir

Research in context

Evidence before this study

The medical and research community are actively exploring the use of oral antiviral drugs in patients with COVID-19 to lower their risk of hospitalisation and death, and to reduce burden on health-care systems. We searched PubMed for studies until 1 November 2023, using the terms "renal failure OR renal impairment OR end stage kidney disease OR dialysis or advanced kidney disease" AND "paxlovid OR nirmatrelvir", without language restrictions. Most studies are case series. One prospective study comprising of 85 patients with renal impairment (eGFR <30 ml/min per 1.73 m^2) showed that the use of nirmatrelvir-ritonavir in this group of patients was well tolerated and safe. Yet, data on comparison between nirmatrelvir-ritonavir and molnupiravir is not available.

Added value of this study

To the best of our knowledge, this study is the one of the first real-world studies to compare nirmatrelvir-ritonavir with molnupiravir in advanced kidney disease during a pandemic wave dominated by the SARS-CoV-2 omicron BA.2 variant and BA.5 variant.

We conducted a territory-wide, observational study to identify the incidence of all-cause mortality among COVID-19 infected advanced kidney disease patients at 90 days post-treatment, the association between mortality and the antiviral drug use, and the complication rate associated with the respective antiviral drugs. Nirmatrelvir-ritonavir was associated with significant reduced risk of all-cause mortality at 90 days. Nirmatrelvir-ritonavir was also significantly associated with a decreased risk of hospitalisation.

Implications of all the available evidence

The study showed that nirmatrelvir-ritonavir was associated with lower mortality than molnupiravir and was not associated with an increased risk of adverse clinical outcomes. Nirmatrelvir-ritonavir is safe in patients with chronic kidney disease and is likely associated with better clinical outcomes than molnupiravir.

Introduction

Near seven million people have died globally from coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Hong Kong had been seriously hit by the fifth wave of COVID-19 caused by the Omicron variant BA.2 and BA.5 since 31 December 2021. Over 13 months, 2.8 millions of Hong Kong citizens were tested positive for SARS-CoV-2.[2] The reported mortality rate of 37.7 per million population was one of the highest worldwide.[3] The peritoneal dialysis and hemodialysis populations had high mortality with 19.4 and 21.9 deaths per 1000 dialysis population, respectively.[4] Patients with chronic kidney disease (CKD) are likely to have worse outcome including higher incidence of hospitalisation.[5,6] Early effective antiviral therapy is therefore crucial for this group of patients. Nirmatrelvir-ritonavir and molnupiravir have been widely used in Hong Kong since their availability. Nirmatrelvir is a protease inhibitor. It is 70% protein bound and excretion is 35% through the

kidneys.[7] Ritonavir is given together to enhance bioavailability of nirmatrelvir. Unlike nirmatrelvir, ritonavir is metabolised mainly in the liver. Nirmatrelvir is dosed at 300 mg twice a day for eGFR ≥60 ml/min per 1.73 m^2 and 150 mg twice a day for eGFR ≥30 to <60 ml/min per 1.73 m^2. Nirmatrelvir-ritonavir is an effective anti-viral that has been shown to reduce hospitalisation or death by day 28 in EPIC-HR trial.[8] Yet, patients with advanced kidney disease (CKD stage 4, i.e., eGFR <30 ml/min per 1.73 m^2) were excluded from the trial because of theoretical concern about drug safety as accumulation of nirmatrelvir is expected in patients with impaired renal function. In the product monograph, it is stated that the drug is 'not recommended' for those with an eGFR <30 ml/min per 1.73 m^2.[8] Molnupiravir, on the other hand, is safe for patients with CKD stage 4 or above, including those on dialysis. It has been the conventional oral antiviral drug for this group of vulnerable high-risk patients. Molnupiravir inhibits viral replication by promoting widespread viral mutation when its metabolite incorporated into the SARS-CoV-2 RNA. In MOVe-OUT trial, it has been shown that early treatment with molnupiravir, when compared with placebo, reduced the risk of hospitalisation or death in at-risk, unvaccinated patients with COVID-19.[9] However, among high-risk vaccinated adults in the community, Butler et al. showed that molnupiravir did not reduce the frequency of COVID-19-associated hospitalisation or death.[10] Efficacy of molnupiravir in vaccinated adults is therefore a concern. Before another effective antiviral drug is discovered, nirmatrelvir-ritonavir is perhaps a feasible treatment option in patients with CKD stage 4 and above as demonstrated by a prospective trial in Hong Kong. Effectiveness of viral load suppression and the clinical outcome in terms of symptoms resolution were similar to those with better renal function.[11] For molnupiravir, several case series have also demonstrated its safety. While individual antiviral has been demonstrated to be safe in advanced kidney disease, studies regarding direct comparison between nirmatrelvir-ritonavir and molnupiravir is lacking.[12,13] Here, we take another perspective to compare the safety profile and efficacy between nirmatrelvir-ritonavir and molnupiravir in advanced kidney disease.

Methods

Data sources

Clinical data was acquired from the Hospital Authority's (HA) routine electronic health record database, vaccination and confirmed COVID-19 case records were acquired from the Department of Health (DH) of the Government of the Hong Kong Special Administrative Region (HKSAR), and death records were extracted from the Hong Kong Deaths Registry. These databases were integrated by anonymised unique patient identifiers. The HA in Hong Kong manages all public inpatient services and most public outpatient services. Electronic health record database managed by HA contains information on demographics, diagnoses, prescriptions, and laboratory tests of patient, which provide real-time data to support clinical management across all clinics and hospitals within the HA. Vaccination records for all individuals in Hong Kong are maintained by the DH, in which confirmed COVID-19 cases are documented based on both mandatory and voluntary reporting of positive Polymerase Chain Reaction (PCR) and Rapid Antigen Test (RAT) results. Deaths Registry is a government agency under the HKSAR government which maintains records of all registered deaths for all residents in Hong Kong. These population-based databases have been widely utilised in previous studies evaluating the effectiveness of COVID-19 drugs and vaccinations.[14–22] As this was a retrospective observational study, there was no informed consent required. Data was analysed without accessing the patients' particulars including names and identity card numbers.

Study design and eligibility criteria

This study was a target trial emulation using territory-wide electronic health record databases in Hong Kong. Target trial emulation was adopted to reduce some typical challenges in observational studies such as immortal time and selection biases.[23–25] The specification and emulation of the target trial is detailed in Supplementary Table S1. The subject inclusion period commenced from 16 March 2022 (when both molnupiravir and nirmatrelvir-ritonavir became available in Hong Kong) to 31 December 2022, during which there was an outbreak of Omicron BA.2 and its subvariants in Hong Kong.[26] Patients aged ≥18 years who had COVID-19 infection (documented as a PCR/RAT positive result confirmed by DH), received COVID-19 oral antivirals (molnupiravir or nirmatrelvir-ritonavir) within five days, and advanced kidney disease (history of eGFR <30 ml/min per 1.73 m^2) before index date were eligible. The index date was defined as the date of molnupiravir or nirmatrelvir-ritonavir prescription. Exclusion criteria include: patients who (i) had a history of COVID-19 infection before index date, (ii) on remdesivir, tocilizumab, baricitinib and interferon beta-1b within 90 days before index date, (iii) hospitalised at least 5 days before index date, (iv) admitted to intensive care unit (ICU) or received ventilatory support on or before index date, (v) received first drug treatment >5 days after COVID-19 diagnosis, and (vi) with contraindications to nirmatrelvir-ritonavir or molnupiravir,[27,28] including severe liver impairment (cirrhosis, hepatocellular carcinoma, or liver transplant), and use of interacting drugs (i.e., amiodarone, apalutamide, rifampicin, rifapentine, carbamazepine, primidone, phenobarbital, or phenytoin, direct oral anticoagulants) within 90 days before index date. During the analysis of each outcome, patients who had a history of the outcomes before index date were also excluded.

Sequence trial emulation

A sequence trial approach was adopted to compare the risk of outcomes between patients who received nirmatrelvir-ritonavir and patients who received molnupiravir.[29,30] On each week during the subject inclusion period, each eligible patient newly prescribed with molnupiravir was matched with up to 4 eligible patients newly prescribed with nirmatrelvir-ritonavir, using propensity score matching with caliper of 0.1 to emulate randomisation of treatment assignment. Propensity scores were estimated using logistic regression to predict the probability of treatment assignment given the following baseline covariates: age, sex, number of COVID-19 vaccine doses received, Charlson Comorbidity Index (CCI), hospitalisation, eGFR, renal replacement therapy, pre-existing comorbidities (cancer, respiratory disease, myocardial infarction, ischaemic stroke, diabetes, 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 H_2 receptor antagonists, monoclonal antibody infusion) within past 90 days. These covariates were selected since they were potential confounders of COVID-19 oral antiviral treatments and mortality. Individuals were followed up from the index date until the earliest outcome occurrence, death, 90 days from index date or the end of data availability.

Outcomes

Effectiveness outcomes included occurrence of (i) all-cause mortality, (ii) ICU admission, (iii) ventilatory support, (iv) hospitalisation, (v) hepatic impairment, (vi) ischaemic stroke, and (vii) myocardial infarction within 90 days after the index date. Use of ventilatory support was identified using International Classification of Diseases, Ninth Revision (ICD-9) procedure codes (39.65, 89.18, 93.90, 93.95, 93.96, 96.7, 96.04). Hepatic impairment was defined as patients who fulfil the criteria for any level of severity (mild, moderate, moderate to severe, severe) of drug induced liver injury. The level of severity is categorised based on the International Drug-Induced Liver Injury (DILI) Expert Working Group classification.[31] According to the Asia Pacific Association of Study of Liver consensus guidelines,[32] the upper limit of normal (ULN) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were defined as 40 U/L, 40 U/L, and 135 U/L, respectively.[33] Ischaemic stroke was defined based on ICD-9-CM codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434, 436, 437.0, and 437.1. Myocardial infarction was defined based on ICD-9-CM codes 410.

Statistical analysis

Covariate balance in the matched cohort was assessed where a standardised mean difference (SMD) between groups of 0.1 or less for all covariates was considered acceptable.[34] Incidence rates were reported with 95% confidence intervals estimated based on Poisson distribution. Stratified Cox proportional hazards regression adjusted with baseline covariates, which were the same as those used in logistic regression in propensity score matching, were used to compare the risk of outcomes between molnupiravir recipients and nirmatrelvir-ritonavir recipients. Hazard ratios (HR) with 95% confidence intervals were reported. When conducting analysis for each individual outcome (hepatic impairment, ischaemic stroke, and myocardial infarction), patients with a corresponding history of those outcomes at baseline were excluded from the analysis. Absolute risk reduction (ARR) was reported as the difference in rate of events for nirmatrelvir-ritonavir recipients as compared with molnupiravir recipients.

Four sensitivity analyses were performed to evaluate the robustness of the findings from the main analysis. Firstly, the risks of outcomes among patients with COVID-19 who received COVID-19 drug treatments within three days instead of five days were compared. Secondly, the risk of outcomes for patients with COVID-19 receiving nirmatrelvir-ritonavir was compared with molnupiravir who have received vaccination within 180 days prior to first COVID-19 infection. Patients who received vaccination beyond 180 days were considered non-vaccinated. Thirdly, E-value was computed to assess the robustness of conclusions to potential unmeasured confounding. E-value was calculated by formula $RR + \sqrt{RR \times (RR - 1)}$, in which RR = HR for rate of event <15% and $RR = (1–0.5^{\sqrt{HR}})/(1–0.5^{\sqrt{1/HR}})$ for rate of event over 15%. It is a measurement of the minimal strength required for a confounder to be associated with both treatment and outcome to fully explain away the observed association between treatment and outcome.[35] Lastly, all-cause mortality was adjusted as competing risk, in which competing risk Cox regression was performed.

There was no missing data from the dataset. Comorbidity, medication, and vaccination were defined based on the availability of record. All statistical tests were two-sided, with p-values below 0.05 deemed statistically significant. Statistical analyses were performed using R version 4.0.3 (www.R-project.org). To ensure transparent reporting of the cohort study, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist was followed.

Ethics statement

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

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

After applying the eligibility criteria and matching, 4886 (nirmatrelvir-ritonavir: 1462; molnupiravir: 3424) patients were included (Fig. 1). The mean (SD) age and proportion of male were 79.82 (12.21) years and 46.6% for nirmatrelvir-ritonavir recipients, and 79.61 (13.52) years and 46.4% for molnupiravir recipients (Table 1). All baseline characteristics except for eGFR (SMD: 0.144) were well-balanced between groups with SMD <0.1 (Table 1). The baseline characteristics of non-matched and matched eligible patients with COVID-19 in each treatment groups were displayed in Supplementary Table S2. The baseline characteristics of eligible patients before matching were also shown in Supplementary Table S3.

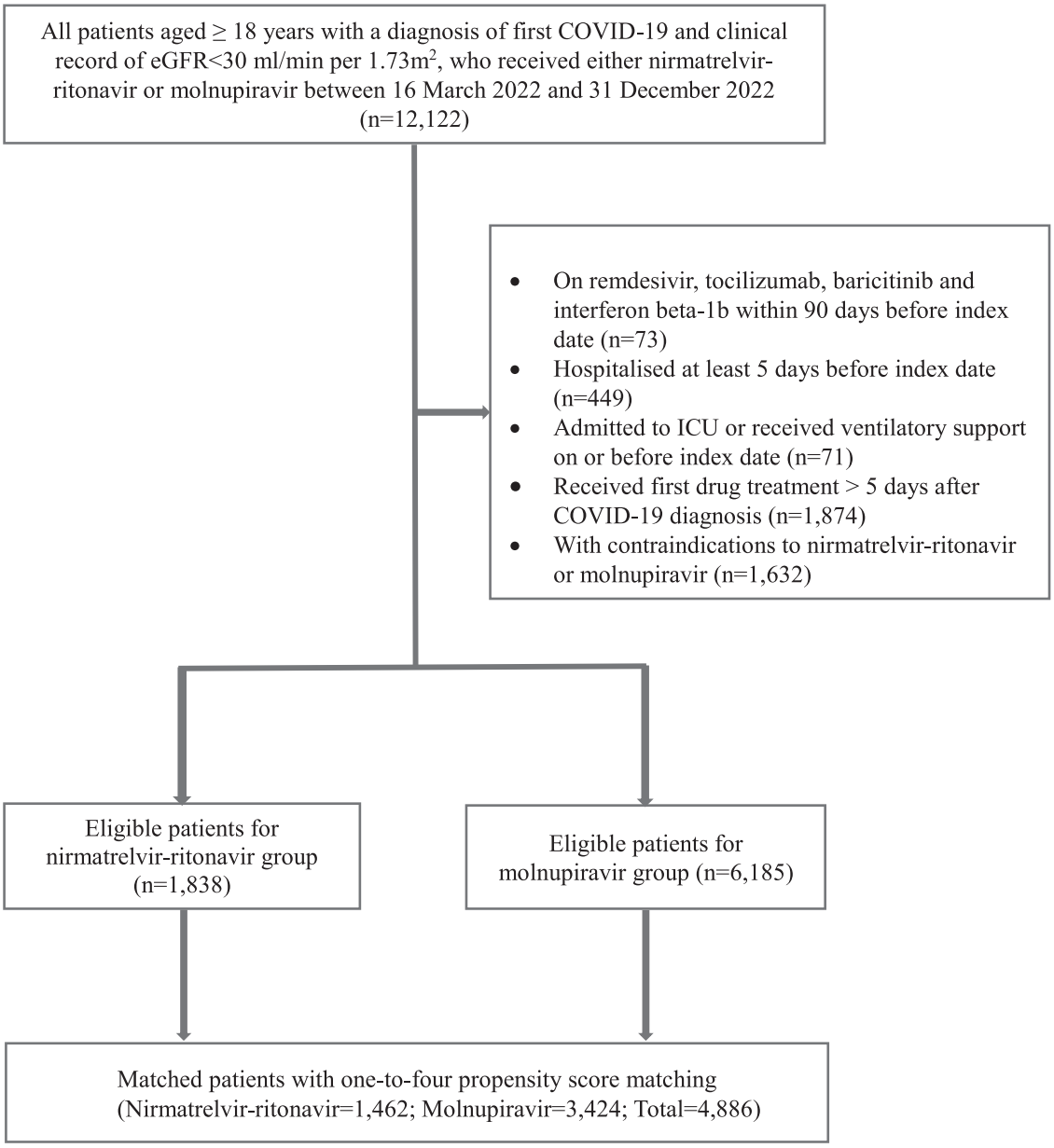

Fig. 1: **Study flow diagram**. Notes: The patients were matched by gender, age, Charlson Comorbidity Index, vaccination status, hospitalisation, eGFR, renal replacement therapy and pre-existing comorbidities and medication use within 90 days at baseline.

Characteristics	Total (N = 4886)		
	Molnupiravir (N = 3424)	Nirmatrelvir-ritonavir (N = 1462)	SMD[a]
Age, year–mean (SD)	79.61 (13.52)	79.82 (12.21)	0.016
Sex, Male (%)	1594 (46.6)	681 (46.6)	0.001
CCI–mean (SD)	5.25 (1.94)	5.21 (2.02)	0.023
COVID-19 vaccination status (%)			0.028
Unvaccinated	408 (11.9)	169 (11.6)	
1 dose	136 (4.0)	54 (3.7)	
2 doses	430 (12.6)	175 (12.0)	
≥3 doses	2450 (71.6)	1064 (72.8)	
Hospitalisation (%)	1228 (35.9)	553 (37.8)	0.041
eGFR, <15 ml/min/1.73 m^2 (%)*	490 (14.3)	141 (9.6)	0.144
Renal replacement therapy	262 (7.7)	81 (5.5)	0.085
Pre-existing comorbidities (%)			
Cancer	310 (9.1)	159 (10.9)	0.061
Respiratory disease	253 (7.4)	114 (7.8)	0.015
Myocardial infarction	222 (6.5)	84 (5.7)	0.031
Ischaemic stroke	224 (6.5)	91 (6.2)	0.013
Diabetes	1624 (47.4)	713 (48.8)	0.027
Hypertension	2419 (70.6)	1052 (72.0)	0.029
Medication use within 90 days (%)			
Renin-angiotensin-systemagents	1795 (52.4)	777 (53.1)	0.014
Beta blockers	1201 (35.1)	477 (32.6)	0.052
Calcium channel blockers	2150 (62.8)	885 (60.5)	0.046
Diuretics	968 (28.3)	347 (23.7)	0.104
Nitrates	472 (13.8)	193 (13.2)	0.017
Lipid lowering agents	2097 (61.2)	892 (61.0)	0.005
Insulins	630 (18.4)	239 (16.3)	0.054
Antidiabetic drugs	1331 (38.9)	579 (39.6)	0.015
Antiplatelets	1502 (43.9)	621 (42.5)	0.028
Immunosuppressants	96 (2.8)	32 (2.2)	0.039
Corticosteroids	240 (7.0)	89 (6.1)	0.037
Proton pump inhibitors	1622 (47.4)	657 (44.9)	0.049
Histamine H_2 receptor antagonists	809 (23.6)	354 (24.2)	0.014
Monoclonal antibody infusion	2 (0.1)	1 (0.1)	0.004

SMD, Standardised mean difference; SD, Standard deviation; CCI, Charlson Comorbidity Index. [a]SMD <0.1 indicates balance between groups.

Table 1: **Baseline characteristics of eligible COVID-19 patients with advanced kidney disease after one-to-four propensity score matching.**

The 90-day cumulative incidence of outcomes between groups were shown in Fig. 2. In this study, 347 events of all-cause mortality (nirmatrelvir-ritonavir: 74, 5.06%; molnupiravir: 273, 7.97%), 836 events of hospitalisation (nirmatrelvir-ritonavir: 218, 23.98%; molnupiravir: 618, 28.14%), 10 events of ICU admission (nirmatrelvir-ritonavir: 4, 0.27%; molnupiravir: 6, 0.18%), 48 events of ventilatory support (nirmatrelvir-ritonavir: 13, 0.89%; molnupiravir: 35, 1.02%), 1 events of hepatic impairment (nirmatrelvir-ritonavir: 0, 0%; molnupiravir: 1, 0.03%), 8 events of ischaemic stroke (nirmatrelvir-ritonavir: 3, 0.22%; molnupiravir: 5, 0.16%) and 9 events of myocardial infarction (nirmatrelvir-ritonavir: 2, 0.15%; molnupiravir: 7, 0.22%) were observed (Table 2).

Nirmatrelvir-ritonavir users had lower rates of all-cause mortality (absolute risk reduction (ARR) at 90 days 2.91%, 95% CI: 1.47–4.36%) and hospitalisation (ARR at 90 days 4.16%, 95% CI: 0.81–7.51%) as compared with molnupiravir users. Similar rates of ICU admission (ARR at 90 days –0.09%, 95% CI: –0.4 to 0.2%), ventilatory support (ARR at 90 days 0.13%, 95% CI: –0.45 to 0.72%), hepatic impairment (ARR at 90 days 0.03%, 95% CI: –0.03 to 0.09%), ischaemic stroke (ARR at 90 days –0.06%, 95% CI: –0.35 to 0.22%), and myocardial infarction (ARR at 90 days 0.07%, 95% CI: –0.19 to 0.33%) were found between nirmatrelvir-ritonavir and molnupiravir users (Table 2). Consistent results were observed in relative risk adjusted with baseline characteristics. Nirmatrelvir-ritonavir was

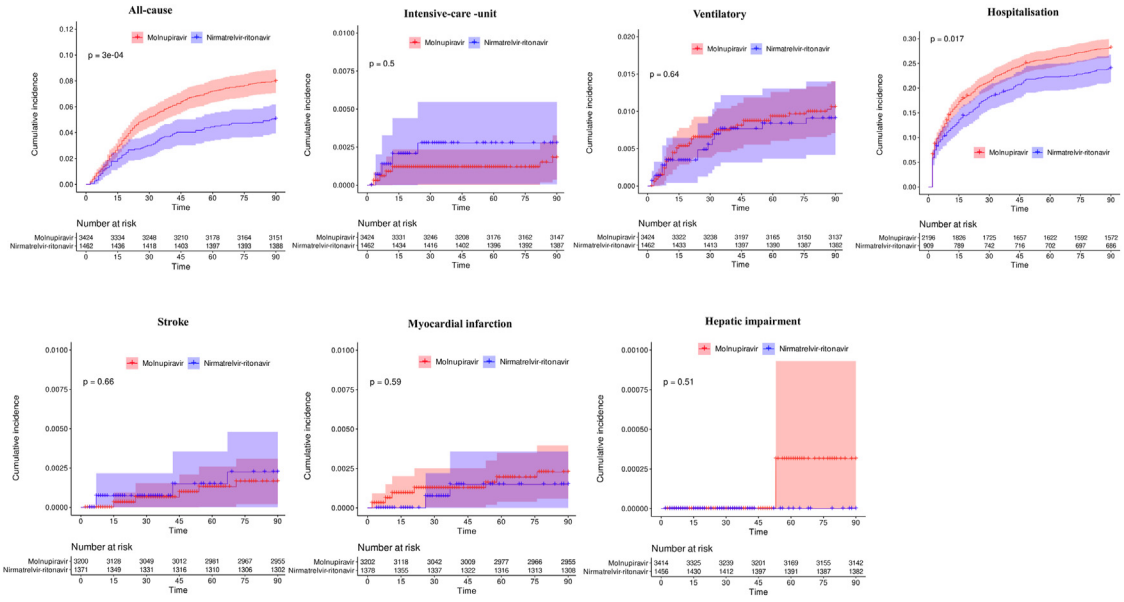

Fig. 2: **90-day cumulative incidence of outcomes.**

associated with significantly reduced risk of all-cause mortality (HR: 0.624, 95% CI: 0.455–0.857) and hospitalisation (HR: 0.782, 95% CI: 0.64–0.954) (Table 2).

The HR for all-cause mortality were largely consistent in subgroup analysis (Table 3). Sensitivity analysis on 1) patients with COVID-19 received COVID-19 drug treatments within three days from diagnosis and 2) patients with COVID-19 receiving vaccination within 180 days prior to first COVID-19 infection showed similar results as the main analysis (Supplementary Tables S4 and S5). Based on the estimated HR of all-cause mortality (HR: 0.624), the E-value was 2.59. This suggested that the estimated HR could be explained by unmeasured confounding variables with 2.59-fold stronger association with all-cause mortality. Hence, our conclusions are likely robust to potential unmeasured confounding (Supplementary Table S6). The HRs for ventilatory support (HR: 0.871, 95% CI: 0.456–1.663) and hospitalisation 0.874 (0.770, 0.993) were also consistent with main analysis after adjusted with all-cause mortality in competing risk analysis (Supplementary Table S7).

Discussion

In this observational study, we showed that patients with COVID-19 and advanced CKD (eGFR <30 ml/min per 1.73 m^2) who received nirmatrelvir-ritonavir had lower

Outcomes	Total (N = 4886)								ARR (95% CI) (%)	Adjusted HR (95% CI)[a]
	Nirmatrelvir-ritonavir (N = 1462)				Molnupiravir (N = 3424)					
	Events	Rate (%)	Follow-up time (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up time (days)	Incidence rate (per 10,000 person days)		
All-cause mortality	74	5.06	127,047	5.82 (4.57, 7.31)	273	7.97	291,056	9.38 (8.30, 10.56)	2.91 (1.47, 4.36)	0.624 (0.455–0.857)
ICU admission	4	0.27	126,933	0.32 (0.09, 0.81)	6	0.18	290,866	0.21 (0.08, 0.45)	−0.09 (−0.40, 0.20)	NA[b]
Ventilatory support	13	0.89	126,588	1.03 (0.55, 1.76)	35	1.02	290,024	1.21 (0.84, 1.68)	0.13 (−0.45, 0.72)	0.547 (0.124–2.407)
Hospitalisation	218	23.98	66,252	32.90 (28.68, 37.57)	618	28.14	153,343	40.30 (37.19, 43.61)	4.16 (0.81, 7.51)	0.782 (0.64–0.954)
Hepatic impairment	0	0.00	126,507	0.00 (0.00, 0.29)	1	0.03	290,236	0.03 (0.00, 0.19)	0.03 (−0.03, 0.09)	NA[b]
Ischaemic stroke	3	0.22	119,199	0.25 (0.05, 0.74)	5	0.16	272,990	0.18 (0.06, 0.43)	−0.06 (−0.35, 0.22)	NA[b]
Myocardial infarction	2	0.15	119,761	0.17 (0.02, 0.60)	7	0.22	272,596	0.26 (0.10, 0.53)	0.07 (−0.19, 0.33)	NA[b]

ARR, Absolute risk reduction; HR, Hazard ratio; CI, Confidence interval; ICU, Intensive care units; NA, Not applicable. [a]Hazard ratios were obtained from stratified Cox proportional hazard regression adjusted by sex, age, Charlson Comorbidity Index, vaccination status, hospitalisation, eGFR, renal replacement therapy, pre-existing comorbidities and medication use within 90 days at baseline. [b]Not applicable due to insufficient events observed.

Table 2: **Risk of outcomes for eligible COVID-19 patients with advanced kidney disease receiving nirmatrelvir-ritonavir compared with molnupiravir.**

Subgroups	Total (N = 4886)										
	Nirmatrelvir-ritonavir (N = 1462)				Molnupiravir (N = 3424)				ARR (95% CI) (%)	Adjusted HR (95% CI)[a]	p-value for interaction
	Events	Rate (%)	Follow-up time (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up time (days)	Incidence rate (per 10,000 person days)			
All-cause mortality											
Age, years											0.127
<70	6	2.24	23,828	2.52 (0.92, 5.48)	14	2.03	61,289	2.28 (1.25, 3.83)	−0.21 (0.09, 3.22)	NA[b]	
≥70	68	5.70	103,219	6.59 (5.12, 8.35)	259	9.48	229,767	11.27 (9.94, 12.73)	3.78 (1.62, 6.12)	0.566 (0.401–0.798)	
Sex											0.227
Male	41	6.02	58,868	6.96 (5.00, 9.45)	137	8.59	135,116	10.14 (8.51, 11.99)	2.57 (0.32, 4.83)	0.873 (0.468–1.631)	
Female	33	4.23	68,179	4.84 (3.33, 6.80)	136	7.43	155,940	8.72 (7.32, 10.32)	3.20 (1.35, 5.06)	0.571 (0.265–1.229)	
CCI											0.894
≤5	35	3.88	79,095	4.43 (3.08, 6.15)	115	5.86	169,545	6.78 (5.60, 8.14)	1.98 (0.35, 3.61)	0.614 (0.321–1.174)	
>5	39	6.96	47,952	8.13 (5.78, 11.12)	158	10.81	121,511	13.00 (11.05, 15.20)	3.85 (1.21, 6.49)	0.772 (0.402–1.482)	
COVID-19 vaccination status											0.326
0–1 dose	15	8.88	14,411	10.41 (5.83, 17.17)	62	15.20	33,051	18.76 (14.38, 24.05)	6.32 (0.80, 11.85)	NA[b]	
≥2 doses	59	4.56	112,636	5.24 (3.99, 6.76)	211	7.00	258,005	8.18 (7.11, 9.36)	2.44 (0.98, 3.89)	0.549 (0.372–0.81)	

HR, Hazard ratio; CI, Confidence interval; CCI, Charlson Comorbidity Index. [a]Hazard ratios were obtained from stratified Cox proportional hazard regression adjusted by sex, age, Charlson Comorbidity Index, vaccination status, hospitalisation, eGFR, renal replacement therapy, pre-existing comorbidities and medication use within 90 days at baseline. [b]Not applicable due to insufficient events observed.

Table 3: **Subgroup analyses of all-cause mortality.**

all-cause mortality at day 90 after treatment than those who received molnupiravir. Between nirmatrelvir-ritonavir and molnupiravir, the use of nirmatrelvir-ritonavir was associated with a lower hospitalisation rate. The two treatment arms had similar ICU admission rates and rates of complications including hepatic impairment, respiratory and cardiovascular incidents.

Effective anti-viral therapy has been recommended for patients with COVID-19 who are at risk of clinical deterioration, with CKD being one of the major risk factors. However, the use of nirmatrelvir has been limited among patients with CKD based on its renal excretion. Patients with eGFR <30 ml/min per 1.73 m^2 were not included in the EPIC-HR trial, and thus clinical data regarding its safety and effectiveness has been scant. In patients with better renal function, the safety profile of nirmatrelvir was reported to be favorable with minimal serious adverse effects. The nirmatrelvir-ritonavir group even had a lower rate of serious adverse events (2%) than in the placebo group (7%).[8] In patients with more advanced kidney disease, nirmatrelvir serum concentration is inevitably higher.[36] The maximum tolerated dose of nirmatrelvir in humans remains a question. One animal study found no adverse effects even when nirmatrelvir was dosed at 1000 mg/kg per day, which was equivalent to 8 times the recommended dose in humans.[7] Peak plasma concentration of nirmatrelvir-ritonavir in patients receiving intermittent haemodialysis can be up to 4 times of that in patients with normal renal function.[37] Hepatotoxicity is one of the side effects of nirmatrelvir and hence hepatic tolerance is one of the concerns when dosing in patients with advanced kidney disease.[7] Lingscheid et al. reported a case series of treatment of nirmatrelvir-ritonavir in 4 patients with end-stage kidney disease requiring intermittent haemodialysis. None of the patients developed hepatic impairment after receiving nirmatrelvir-ritonavir (150 mg nirmatrelvir + 100 mg ritonavir twice daily for 5 days).[37] Similar study on patients receiving intermittent haemodialysis showed that nirmatrelvir-ritonavir was in general well tolerated without hepatic impairment reported.[38] Our study concurred with the issue of hepatotoxicity that both treatment arms of nirmatrelvir-ritonavir and molnupiravir had similar rates of hepatic impairment. Regarding efficacy, Hiremath et al. prescribed a modified regimen of nirmatrelvir-ritonavir suggested by a group of Canadian physicians to dialysis patients (300 mg nirmatrelvir + 100 mg ritonavir on day 1 then 150 mg nirmatrelvir + 100 mg ritonavir, dose after dialysis for those on haemodialysis).[39] Most patients (96%) were able to complete the regimen and there were no deaths at day 30.[40] Our study further compared the efficacy of nirmatrelvir-ritonavir with molnupiravir and showed that the former was associated with a lower all-cause mortality than the latter.

Patients with dysphagia and those who required enteral tube feeding were not excluded from the analysis. In the product monograph, it stated that the drugs cannot be chewed or crushed and must be swallowed whole.[28] It was remarked by the manufacturer that this was based on a lack of data support. Yet there was preliminary data supporting crushing nirmatrelvir.[41] In Hong Kong, administering crushed nirmatrelvir-ritonavir has been practised widely as it was recommended by the HA Task Force on Clinical Management on Infection.[42] The more

frail elderly patients who had swallowing difficulty or were on enteral tube feeding were not contraindicated to use of nirmatrelvir-ritonavir. Therefore, enteral tube feeding itself is not a factor contributing to bias in choosing antiviral.

Our study has several strengths and limitations. For the strengths, it is the first territory-wide real-world study comparing nirmatrelvir-ritonavir and molnupiravir in advanced kidney disease. Our findings supplement further pieces of information on how the two antiviral drugs compare to each other in terms of effectiveness. The large electronic health record database in Hong Kong confers high population representation. The use of sequence trial approach helps synchronise eligibility and treatment assignment and mitigate the bias encountered in observational study.

There are several limitations in our study. Firstly, the date of symptom onset is not available and the date of positivity of PCR/RAT is used as a proxy. Individuals may not test themselves unless they develop symptoms. Yet, during the time when compulsory testing was prevalent in Hong Kong in 2022, with strict isolation policy still in place, the number of COVID-19 testing was exceptionally high in the city and regular PCR/RAT testing might pick up the diagnosis earlier than the symptom onset for those whose symptoms were mild or vague, rendering it a reliable proxy for symptom onset.[43] Secondly, the dose of nirmaltrevir-ritonavir is not standardised. Local practice has adopted different dosing strategies (e.g. nirmatrelvir-ritonavir 150 mg/100 mg twice daily for 5 days or the modified dose as suggested by the Canadian group[39]). The performance of each dosing strategy might differ. Thirdly, there exists potential unmeasured confounding which are not available from the dataset. Specifically, the lower CI of E-value (1.22) for hospitalisation may indicate the result might not be robust upon adjustment by existing baseline covariates. The effect of potential residual bias could not be eliminated. Fourthly, information from the electronic health record database is insufficient to categorise COVID-19 related hospitalisation, COVID-19 related mortality and severe COVID-19 among the outcomes. Lastly, subgroups of CKD are not particularly analysed. Dialysis and non-dialysis patients are likely to have different drug elimination profiles. Moreover, pharmacokinetics is dependent on modalities and frequency of dialysis. Whether nirmatrelvir is dialysable or requires further dose adjustments remains to be an area to explore.

In conclusion, treatment with nirmatrelvir-ritonavir in patients with advanced kidney disease was associated with a lower all-cause mortality and hospitalisation than in molnupiravir. Nirmatrelvir-ritonavir had a similar complication rate when compared with molnupiravir. Therefore, nirmatrelvir-ritonavir remains a favourable option for this group of patients. Further research on the difference in pharmacokinetics of nirmatrelvir-ritonavir between dialysis and non-dialysis groups of patients may be needed for better optimising the dosing in each group of patients.

Contributors

WMC, EYFW, ZCTW, ART, ICKW, EWYC and IFNH contributed to the conception and design of the study. performed data acquisition. WMC, EYFW and ZCTW performed data analysis and interpretation. WMC and EYFW wrote the first draft of the manuscript. WMC, EYFW and IFNH accessed and verified the underlying data. All authors revised the manuscript critically for important intellectual content.

Data sharing statement

Data will be available upon request from the Hospital Authority and the Department of Health of Hong Kong SAR via the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data).

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102620.

References

1 WHO. *WHO coronavirus (COVID-19) dashboard*. WHO; 2023. Available from: https://covid19.who.int. Accessed November 24, 2023.
2 Health CfHPotDo. Latest situation of COVID-19 (as of 29 January 2023). Available from: https://www.chp.gov.hk/files/pdf/local_situation_covid19_en.pdf; 2023. Accessed November 24, 2023.
3 Smith DJ, Hakim AJ, Leung GM, et al. COVID-19 mortality and vaccine coverage - Hong Kong special administrative region, China, january 6, 2022-march 21, 2022. *China CDC Wkly*. 2022;4(14):288–292.
4 Chow KM, Chan JYH, Wong SSH, et al. Impact of COVID-19 on the mortality of dialysis patients and kidney transplant recipients during the Omicron fifth wave in Hong Kong. *Hong Kong Med J*. 2023;29(1):82–83.
5 Russo E, Esposito P, Taramasso L, et al. Kidney disease and all-cause mortality in patients with COVID-19 hospitalized in Genoa, Northern Italy. *J Nephrol*. 2021;34(1):173–183.
6 Jdiaa SS, Mansour R, El Alayli A, Gautam A, Thomas P, Mustafa RA. COVID-19 and chronic kidney disease: an updated overview of reviews. *J Nephrol*. 2022;35(1):69–85.
7 Pfizer. *Fact sheet for healthcare providers: emergency use authorization for paxlovidtm*. FDA; 2023. Available from: https://www.fda.gov/media/155050/download. Accessed November 24, 2023.
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):1397–1408.
9 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):509–520.
10 Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023;401(10373):281–293.
11 Chan GCK, Lui GCY, Wong CNS, et al. Safety profile and clinical and virological outcomes of nirmatrelvir-ritonavir treatment in patients with advanced chronic kidney disease and coronavirus disease 2019 (COVID-19). *Clin Infect Dis*. 2023;77(10):1406–1412.
12 Cho WJ, Harden D, Moreno D, et al. Oral antiviral therapies for COVID-19 in patients with advanced chronic kidney disease or kidney failure. *Nephrol Dial Transplant*. 2023;38(8):1912–1914.
13 Dufour I, Devresse A, Scohy A, et al. Safety and efficiency of molnupiravir for COVID-19 patients with advanced chronic kidney disease. *Kidney Res Clin Pract*. 2023;42(2):275–278.
14 Wan EYF, Chui CSL, Lai FTT, et al. Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. *Lancet Infect Dis*. 2021;21:00451–00455.
15 Chua GT, Kwan MYW, Chui CSL, et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following comirnaty vaccination. *Clin Infect Dis*. 2021;75(4):673–681.
16 Li X, Tong X, Yeung WWY, et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. *Ann Rheum Dis*. 2021;81(4):564–568.
17 Lai FTT, Huang L, Chui CSL, et al. Multimorbidity and adverse events of special interest associated with Covid-19 vaccines in Hong Kong. *Nat Commun*. 2022;13(1):1–8.
18 Lai FTT, Li X, Peng K, et al. Carditis after COVID-19 vaccination with a messenger RNA vaccine and an inactivated virus vaccine: a case–control study. *Ann Int Med*. 2022;175(3):362–370.
19 Lai FTT, Huang L, Peng K, et al. Post-Covid-19-vaccination adverse events and healthcare utilization among individuals with or without previous SARS-CoV-2 infection. *J Intern Med*. 2022;291(6):864–869.
20 Li X, Tong X, Wong ICK, et al. Lack of inflammatory bowel disease flare-up following two-dose BNT162b2 vaccine: a population-based cohort study. *Gut*. 2022;71:2608–2611.
21 Wan EYF, Chui CSL, Wang Y, et al. Herpes zoster related hospitalization after inactivated (CoronaVac) and mRNA (BNT162b2) SARS-CoV-2 vaccination: a self-controlled case series and nested case-control study. *Lancet Reg Health West Pac*. 2022;21:100393.
22 Xiong X, Wong CKH, Au ICH, et al. Safety of inactivated and mRNA COVID-19 vaccination among patients treated for hypothyroidism: a population-based cohort study. *Thyroid*. 2022;32(5):505–514.
23 Hernán MA. Methods of public health research—strengthening causal inference from observational data. *N Engl J Med*. 2021;385(15):1345–1348.
24 Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;19(6):766.
25 Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764.
26 Yang B, Lin Y, Xiong W, et al. Comparison of control and transmission of COVID-19 across epidemic waves in Hong Kong: an observational study. *Lancet Reg Health West Pac*. 2024;43:100969.
27 FDA. *Fact sheet for healthcare providers: emergency use authorization for Lagevrio^{TM} (molnupiravir) capsules*. U.S. Food & Drug Administration; 2023. Available from: https://www.fda.gov/media/155054/download. Accessed November 24, 2023.
28 FDA. *Fact sheet for healthcare providers: emergency use authorization for Paxlovid^{TM}*. U.S. Food & Drug Administration; 2023. Available from: https://www.fda.gov/media/155050/download. Accessed November 24, 2023.
29 Danaei G, Rodríguez LA, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. *Stat Methods Med Res*. 2013;22(1):70–96.
30 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021;384(15):1412–1423.
31 Fontana RJ, Seeff LB, Andrade RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology*. 2010;52(2):730–742.
32 Devarbhavi H, Aithal G, Treeprasertsuk S, et al. Drug-induced liver injury: Asia pacific association of study of liver consensus guidelines. *Hepatol Int*. 2021;15(2):258–282.
33 Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. *J Hepatol*. 2020;73(3):566–574.
34 Cheung KS, Leung WK, Seto WK. Application of Big Data analysis in gastrointestinal research. *World J Gastroenterol*. 2019;25(24):2990–3008.
35 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Int Med*. 2017;167(4):268–274.
36 Toussi SS, Neutel JM, Navarro J, et al. Pharmacokinetics of oral nirmatrelvir/ritonavir, a protease inhibitor for treatment of COVID-19, in subjects with renal impairment. *Clin Pharmacol Ther*. 2022;112(4):892–900.
37 Lingscheid T, Kinzig M, Kruger A, et al. Pharmacokinetics of nirmatrelvir and ritonavir in COVID-19 patients with end-stage renal disease on intermittent hemodialysis. *Antimicrob Agents Chemother*. 2022;66(11):e0122922.
38 Zhang AH, Diao ZL, Wang G, et al. Nirmatrelvir/ritonavir use in patients with COVID-19 on hemodialysis: a case series. *Diagn Microbiol Infect Dis*. 2023;107(3):115969.
39 Hiremath S, McGuinty M, Argyropoulos C, et al. Prescribing nirmatrelvir/ritonavir for COVID-19 in advanced CKD. *Clin J Am Soc Nephrol*. 2022;17(8):1247–1250.
40 Hiremath S, Blake PG, Yeung A, et al. Early experience with modified dose nirmatrelvir/ritonavir in dialysis patients with coronavirus disease 2019. *Clin J Am Soc Nephrol*. 2023;18(4):485–490.
41 (CTC) BCTC, ADVISORY CTRa, (CTRAWG) WG. *Therapeutic brief: crushing nirmatrelvir/ritonavir (paxlovid). 2022 4 July*. 2022.
42 (TFCM) HATFoCMoI. *Interim recommendation on clinical management of adult cases with coronavirus disease 2019 (COVID-19) version 2.4*. 2024.
43 Wong SC, Au AK, Lo JY, et al. Evolution and control of COVID-19 epidemic in Hong Kong. *Viruses*. 2022;14(11):2519.