Viral burden rebound in hospitalised patients with COVID-19 receiving oral antivirals in Hong Kong: a population-wide retrospective cohort study

Carlos K H Wong, Kristy T K Lau, Ivan C H Au, Eric H Y Lau, Leo L M Poon, Ivan F N Hung, Benjamin J Cowling, Gabriel M Leung

Summary

Background Viral rebound after nirmatrelvir–ritonavir treatment has implications for the clinical management and isolation of patients with COVID-19. We evaluated an unselected, population-wide cohort to identify the incidence of viral burden rebound and associated risk factors and clinical outcomes.

Methods We did a retrospective cohort study of hospitalised patients with a confirmed diagnosis of COVID-19 in Hong Kong, China, for an observation period from Feb 26 to July 3, 2022 (during the omicron BA.2.2 variant wave). Adult patients (age ≥18 years) admitted 3 days before or after a positive COVID-19 test were selected from medical records held by the Hospital Authority of Hong Kong. We included patients with non-oxygen-dependent COVID-19 at baseline receiving either molnupiravir (800 mg twice a day for 5 days), nirmatrelvir–ritonavir (nirmatrelvir 300 mg with ritonavir 100 mg twice a day for 5 days), or no oral antiviral treatment (control group). Viral burden rebound was defined as a reduction in cycle threshold (Ct) value (≥3) on quantitative RT-PCR test between two consecutive measurements, with such decrease sustained in an immediately subsequent Ct measurement (for those patients with ≥3 Ct measurements). Logistic regression models were used to identify prognostic factors for viral burden rebound, and to assess associations between viral burden rebound and a composite clinical outcome of mortality, intensive care unit admission, and invasive mechanical ventilation initiation, stratified by treatment group.

Findings We included 4592 hospitalised patients with non-oxygen-dependent COVID-19 (1998 [43·5%] women and 2594 [56·5%] men). During the omicron BA.2.2 wave, viral burden rebound occurred in 16 of 242 patients (6·6% [95% CI 4·1–10·5]) receiving nirmatrelvir–ritonavir, 27 of 563 (4·8% [3·3–6·9]) receiving molnupiravir, and 170 of 3787 (4·5% [3·9–5·2]) in the control group. The incidence of viral burden rebound did not differ significantly across the three groups. Immunocompromised status was associated with increased odds of viral burden rebound, regardless of antiviral treatment (nirmatrelvir–ritonavir: odds ratio [OR] 7·37 [95% CI 2·56–21·26], p=0·0002; molnupiravir: 3·05 [1·28–7·25], p=0·012; control: 2·21 [1·50–3·27], p<0·0001). Among patients receiving nirmatrelvir–ritonavir, the odds of viral burden rebound were higher in those aged 18–65 years (*vs* >65 years; 3·09 [1·00–9·53], p=0·050), those with high comorbidity burden (score >6 on the Charlson Comorbidity Index; 6·02 [2·09–17·38], p=0·0009), and those concomitantly taking corticosteroids (7·51 [1·67–33·82], p=0·0086); whereas the odds were lower in those who were not fully vaccinated (0·16 [0·04–0·67], p=0·012). In patients receiving molnupiravir, those aged 18–65 years (2·68 [1·09–6·58], p=0·032) or on concomitant corticosteroids (3·11 [1·23–7·82], p=0·016) had increased odds of viral burden rebound. We found no association between viral burden rebound and occurrence of the composite clinical outcome from day 5 of follow-up (nirmatrelvir–ritonavir: adjusted OR 1·90 [0·48–7·59], p=0·36; molnupiravir: 1·05 [0·39–2·84], p=0·92; control: 1·27 [0·89–1·80], p=0·18).

Interpretation Viral burden rebound rates are similar between patients with antiviral treatment and those without. Importantly, viral burden rebound was not associated with adverse clinical outcomes.

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Introduction

During the COVID-19 global pandemic, multiple drugs have been repurposed or developed for the treatment of SARS-CoV-2 infection. Ritonavir-boosted nirmatrelvir (nirmatrelvir–ritonavir), which targets the main protease (M^{pro}) of SARS-CoV-2, and molnupiravir, which targets the viral RNA-dependent RNA polymerase, are two oral antiviral drugs that ultimately inhibit viral replication.[1,2] Current guidelines recommend early use (within 5 days of symptom onset) of these oral antivirals in patients with COVID-19 who do not require hospitalisation or supplemental oxygen but are at high risk of progression to severe disease.[3,4] When accessible and clinically appropriate, the use of nirmatrelvir–ritonavir should be prioritised over molnupiravir, given the higher efficacy of nirmatrelvir–ritonavir in preventing hospitalisation or

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For the Chinese translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

The medical and research community are actively exploring the use of oral antivirals in patients with COVID-19 to lower their risks of hospitalisation and death, and to reduce burden on health-care systems. However, there are increasing numbers of anecdotal reports of viral rebound following treatment with nirmatrelvir–ritonavir. We searched Scopus and PubMed for studies published from database inception until Oct 21, 2022, using the terms "SARS-CoV-2 OR COVID-19" AND "molnupiravir OR Lagevrio OR EIDD-2801" OR "nirmatrelvir OR Paxlovid OR PF-07321332" AND "rebound", without language restrictions. Major studies examining COVID-19 rebound or viral load rebound have been case study reports and observational cohort studies. A standard definition of COVID-19 rebound remains to be established. Data from post-marketing surveillance of the oral antivirals being used in clinical practice (nirmatrelvir–ritonavir and molnupiravir) are needed, to identify the incidence of COVID-19 rebound with and without oral antiviral use, to illustrate changes in viral load with time and any association with clinical status, and to identify potential risk factors related to COVID-19 rebound. As yet, population-wide evidence on viral burden rebound in patients receiving and not receiving oral antivirals in clinical practice is absent.

Added value of this study

To the best of our knowledge, this study is the one of the first real-world studies to explore viral burden rebound in patients receiving and not receiving oral antivirals during a pandemic wave dominated by the SARS-CoV-2 omicron BA.2.2 variant. We conducted a territory-wide, retrospective cohort study to identify the incidence of viral burden rebound and associated risk factors, and the association between viral burden rebound and risks of clinical outcomes in Hong Kong. Viral burden rebound occurred in 6·6% of patients receiving nirmatrelvir–ritonavir, 4·8% of patients receiving molnupiravir, and 4·5% of control patients. Immunocompromised status was associated with increased odds of viral burden rebound, regardless of whether antiviral treatment was used or the type of treatment. Among patients receiving nirmatrelvir–ritonavir, the odds of rebound were higher in those aged 18–65 years (*vs* >65 years), those with high comorbidity burden, and those concomitantly taking corticosteroids, while the odds were lower in those who had not been fully vaccinated. Patients taking molnupiravir who were aged 18–65 years or on concomitant corticosteroids had increased odds of rebound. We found no association between viral burden rebound and risk of a composite clinical outcome (mortality, intensive care unit admission, and initiation of invasive mechanical ventilation) after the end of standard treatment.

Implications of all the available evidence

Our cohort study indicated that viral burden rebound was not a common event, although it particularly occurred among patients who were immunocompromised or receiving concomitant corticosteroids. Incidence of viral burden rebound was similar with and without antiviral treatment. Viral burden rebound did not appear to be associated with adverse serious clinical outcomes. Further research is needed to establish a standard definition of COVID-19 rebound for comparison across studies, and to identify the underlying mechanism, and possible variation by timing, dosage, and duration of antiviral therapy.

death when compared with placebo (relative risk reduction of 88% with nirmatrelvir–ritonavir *vs* 30% with molnupiravir).[1–4] Recent observational studies confirmed the clinical benefits of nirmatrelvir–ritonavir during the omicron wave, especially among older patients and patients with pre-existing comorbidities, immunosuppression, or obesity.[5–7] Additionally, analyses in clinical trials have identified a reduced need for respiratory interventions, greater decrease in SARS-CoV-2 RNA load, and faster viral RNA clearance among patients taking molnupiravir versus control groups.[8–10]

Although nirmatrelvir–ritonavir is increasingly prescribed to ambulatory patients with mild-to-moderate COVID-19 in the community, many case reports have described symptom recurrence or re-positive results on RT-PCR or viral antigen test shortly after initial recovery or a negative test after the standard 5-day treatment course.[11] On May 24, 2022, the US Centers for Disease Control and Prevention released a health advisory in response to increasing concerns, recognising that such COVID-19 rebound in which viral load resurges could occur independently of nirmatrelvir–ritonavir use; and given that most cases of viral rebound have been in patients with mild illness, without necessitating any additional treatment, the authority continues to recommend early initiation of nirmatrelvir–ritonavir for patients at high risk of severe COVID-19.[11]

Over a range of 8–19 days after the initial onset of COVID-19, or a median of 4–9 days after completing nirmatrelvir–ritonavir treatment, reported cases of COVID-19 rebound were characterised by the recurrence or worsening of symptoms previously resolved or improved, re-positive RT-PCR or viral antigen tests that had previously turned negative, detectable or even an increase in viral load, and culturable virus indicative of possible infectiousness.[12–17] Evidence of viral rebound after molnupiravir treatment is fairly scarce, although suggests potentially similar incidences of COVID-19 rebound between molnupiravir and nirmatrelvir–ritonavir.[18] Nevertheless, a standard definition of COVID-19 rebound remains to be established. Further data from post-marketing surveillance of both oral antivirals

(nirmatrelvir–ritonavir and molnupiravir) in clinical use are needed, to establish the incidence of COVID-19 rebound with and without oral antiviral use, to illustrate the changes in viral load with time and any association with clinical status, and to identify potential risk factors related to COVID-19 rebound. This observational study aimed to estimate the incidence of viral burden rebound in relation to changes in cycle threshold (Ct) value measurements among patients receiving and not receiving oral antivirals. We also sought to identify potential risk factors of viral burden rebound and examine the clinical outcomes associated with such rebound.

Methods

Study design

In this population-wide retrospective cohort study, we assessed viral burden rebound in hospitalised adult patients (age ≥18 years) with non-oxygen-dependent COVID-19 in public hospitals in Hong Kong, China, for an observation period between Feb 26, 2022 (the date when oral antivirals were first available for use in Hong Kong), and July 3, 2022, during the omicron BA.2.2 variant-dominant period.[19] Previous studies have assessed viral load rebound, on the basis of viral load measurements (ie, viral copies per mL). Here, we defined viral burden rebound on the basis of Ct values, adapted from previous studies.[20,21] The study protocol is available in appendix 2 (pp 26–30). This study was approved by the institutional review board of The University of Hong Kong and Hospital Authority Hong Kong West Cluster (reference number UW 20–493).

Data source and patients

COVID-19 cases were identified from the eSARS data of the Centre for Health Protection, Department of Health of Hong Kong Special Administrative Region. Electronic medical records of hospitalised patients with a confirmed diagnosis of COVID-19 were retrieved from the Hospital Authority of Hong Kong, and included demographic information, disease diagnoses, drug prescriptions, laboratory tests, hospital admission date, and inpatient procedures. Names of hospitals were not shared to maintain patient anonymity. The Hospital Authority data are linked by the Department of Health to their vaccination records with use of unique identification numbers. The linked database hosted by the Hospital Authority has been widely used for studies to evaluate the effectiveness of vaccine and drug treatments for COVID-19.[20,22–24] Given the extraordinary nature of the COVID-19 pandemic, individual patient-informed consent was not required for this retrospective cohort study using anonymised data.

We included patients receiving either molnupiravir (800 mg twice a day for 5 days) or nirmatrelvir–ritonavir (nirmatrelvir 300 mg with ritonavir 100 mg twice a day for 5 days) during the observation period. Completion of the 5-day regimen was not a prerequisite for study inclusion. As all public hospitals in Hong Kong are centrally managed under the Hospital Authority, oral antivirals were prescribed to patients with COVID-19 as clinically appropriate on the basis of the same set of drug treatment guidelines,[25] and both oral antivirals were equally accessible across all public hospitals during the study period (since Feb 26, 2022, for molnupiravir, and since March 16, 2022, for nirmatrelvir–ritonavir). According to the Hospital Authority internal clinical management guidelines for COVID-19,[25] patients with mild symptoms, at risk of progressing to severe disease (ie, diabetes, obesity with a body-mass index ≥30 kg/m², age ≥60 years, immunocompromised state, underlying chronic illnesses, or not fully vaccinated), and at an early stage of disease (within 5 days of symptom onset) were recommended to receive molnupiravir or nirmatrelvir–ritonavir. Later versions (since March 21, 2022, past the wave peak of the omicron wave in early March, 2022) of the guidelines also specified that nirmatrelvir–ritonavir should be preferentially administered over molnupiravir, unless the patient was on any concomitant medication contraindicated for nirmatrelvir–ritonavir.[26] Control patients were selected from the cohort of hospitalised patients with non-oxygen-dependent COVID-19 who did not receive oral antivirals (molnupiravir or nirmatrelvir–ritonavir) during the observation period.

Patients were eligible for inclusion if they had been admitted to hospital within 3 days after their first positive COVID-19 test on quantitative RT-PCR (RT-qPCR) or rapid antigen test, or if they tested positive within 3 days after their admission date (RT-qPCR or rapid antigen test), so as to include patients who were likely to have been admitted to hospital due to SARS-CoV-2 infection. Confirmation of a first-positive test was based on patient-self report or government records. Although not an inclusion requirement, all patients included in our cohort had a Ct value on admission, having done an RT-qPCR test within 3 days before or after admission. We excluded patients who were admitted to hospital before Feb 26, 2022 (the date of first molnupiravir prescription) or after June 26, 2022 (ie, with less than 1 week of follow-up), those aged younger than 18 years, those who received both molnupiravir and nirmatrelvir–ritonavir, and those receiving supplemental oxygen or invasive or non-invasive mechanical ventilation at the start of follow-up (index date). Among patients receiving antiviral treatment, we excluded those without at least one Ct value measurement from real-time RT-qPCR before or during antiviral treatment and at least one Ct value measurement after the end of antiviral treatment. Control patients without a Ct value measurement more than 5 days after the first measurement were also excluded.

See Online for appendix 2

Procedures

Follow-up started from the index date (day 0), defined as the date of first symptom onset, first positive rapid

antigen test or RT-qPCR test, or initiation of molnupiravir or nirmatrelvir–ritonavir, whichever was the earliest. Patients were observed from the index date until registered death, the occurrence of clinical outcome events, or the end of the observation period (July 3, 2022), whichever occurred first.

Baseline data collected from electronic medical records included age, sex, Charlson Comorbidity Index (CCI), immunocompromised status, case classification (imported cases *vs* local cases), COVID-19 vaccination status, concomitant treatment initiated on the day of admission (remdesivir, antibiotics, dexamethasone and other systemic steroids, interferon-β-1b, baricitinib, and tocilizumab), and Ct value on admission. Immunocompromised patients were those with primary immunodeficiency or on active immunosuppressive treatment at baseline or in the past 12 months, with immunosuppressive treatments defined as medications listed under the British National Formulary Chapter 8 (Malignant Disease and Immunosuppression). Fully vaccinated status was defined as having received at least two doses of BNT162b2 (Comirnaty, Pfizer-BioNTech) or three doses of CoronaVac (Sinovac Biotech), and being at least 14 days since the last dose at baseline or the index date.[22] Imported cases were identified among inbound travellers from mandatory RT-qPCR tests conducted upon arrival and during quarantine. Remdesivir plus dexamethasone were indicated when hospitalised patients had moderate symptoms requiring supplemental oxygen, or moderate-to-severe symptoms requiring oxygen through a high-flow device or non-invasive ventilation.[25,26]

For the **British National Formulary Chapter 8** see https://openprescribing.net/bnf/08/

Viral burden rebound was defined as a reduction in observed Ct value larger than or equal to 3 between two consecutive measurements, with this decrease sustained in at least the immediately subsequent Ct measurement (for patients with ≥3 Ct measurements), as follows: ($\Delta Ct=Ct_{[measurement\ 1]}-Ct_{[measurement\ 2]}\geq 3$ and $\Delta Ct=Ct_{[measurement\ 1]}-Ct_{[measurement\ 3]}\geq 3$). Having three or more Ct measurements was not a prerequisite to define viral burden rebound. The Ct values were provided by the SARS-CoV-2 RT-qPCR assays performed in clinical settings of the Hospital Authority. Ct values were used as a proxy of viral burden, given that they are inversely correlated with viral load (ie, a lower Ct value implies a higher viral burden). A decrease in Ct value by approximately 3 units was considered a rough estimate of an eight-times increase in viral RNA, a surrogate marker of viral load.[27] When the RT-qPCR result was negative, Ct value was not available and was imputed with a value of 40, which was treated as the detection limit of the assay.[28]

Outcomes

We compared the incidence of viral burden rebound across the groups, and explored potential predictors of viral burden rebound. We selected risk factors for progression to severe COVID-19 as potential predictors for viral burden rebound, including age (≤65 years or >65 years), sex, CCI (≤6 or >6), vaccination status, use of concomitant corticosteroids, and immunocompromised status.[18] We also studied the association of a composite clinical outcome of mortality, initiation of invasive mechanical ventilation, and intensive care unit (ICU) admission with viral burden rebound, from day 5 of follow-up to the end of follow-up. We also assessed separately the association between viral burden rebound and mortality, and between viral burden rebound and ICU admission or initiation of invasive mechanical ventilation. Patients with a prespecified clinical outcome during the first 4 days from the index date were excluded from analysis.

Statistical analysis

We estimated daily Ct value with a generalised-additive mixed-effects model. The Ct value trajectory was assumed to be identical for all individuals (common slope), whereas the Ct values on the index date were assumed to vary among individuals (random intercept).[29] The Laird-Ware form of the linear mixed model was applied to the log of the Ct value. The Akaike information criterion was used to select the best restricted cubic spline model among models with five knots (appendix 2 p 8).[30] Applying the fitted models, we produced line plots of mean predicted daily Ct value with 95% bootstrap confidence intervals in each group, using 1000 bootstrap samples. Ct value trajectory plots for the first 21 days since the index date, as the reported approximate period over which viral shedding decreases towards the detection limit,[31] were stratified by age group (≤65 or >65 years), CCI score (≤6 or >6), and vaccination status.[20] Considering that viral burden rebound could be dependent on the timing and frequency of RT-qPCR tests, we explored the effect of such potential surveillance bias on daily Ct values among those with early or more frequent RT-qPCR tests (more than three Ct value measurements within 7 days and 14 days since the index date), and those with later or less frequent testing (three or fewer Ct value measurements in the same periods). Baseline characteristics were also compared between hospitalised patients with repeated (two or more) RT-qPCR measurements (included in our cohort) and those without repeated RT-qPCR measurements (excluded from our cohort), to identify if potential biases associated with non-random repeated RT-qPCR measurements would have affected the interpretation of our findings.

The incidence of viral burden rebound in the molnupiravir, nirmatrelvir–ritonavir, and control groups was estimated. 95% CIs for estimates were calculated with the logit transformation method for binomial proportion confidence intervals. Potential predictors for viral burden rebound were assessed by logistic regression.

To assess the potential association between viral burden rebound and the prespecified clinical outcomes, odds ratios (ORs) with 95% CIs were estimated by multivariable logistic regression, adjusting for the baseline covariables

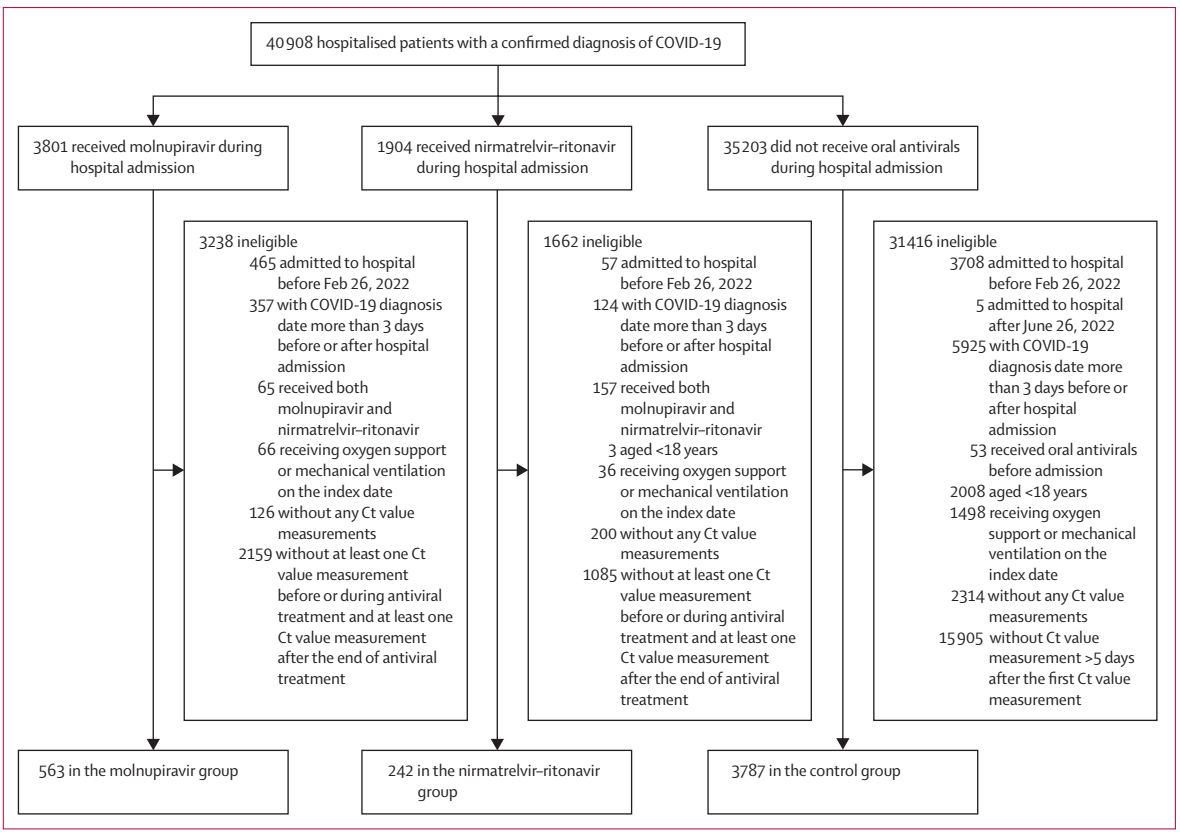


Figure 1: **Identification of patients receiving molnupiravir or nirmatrelvir–ritonavir and control patients**
Eligible patients were identified among those admitted to hospital with COVID-19 not requiring oxygen therapy from Feb 26 to July 3, 2022 in Hong Kong, China. Ct=cycle threshold.

of age, sex, pre-existing comorbidities, vaccination status, concomitant treatments initiated, and Ct value on admission. A post-hoc logistic regression adjusting for these baseline covariables was also conducted to compare the incidence of viral burden rebound among the three groups. As a sensitivity analysis, we used a case-control design to estimate the adjusted OR for viral burden rebound occurring 28 days before a reference date between patients with and without the composite outcome. Viral burden rebound was observed within 28 days before the occurrence of clinical outcomes for cases, and within 28 days since the index date for controls; thus, both cases and controls had a unified 28-day observation time for the analysis (appendix 2 p 3). We also performed sensitivity analyses of the association between viral burden rebound and clinical outcomes by: stratifying the timing and frequency of RT-qPCR tests performed during the first 1 or 2 weeks of follow-up (ie, more than three *vs* three or fewer Ct value measurements); adjusting for the date of admission and study period (restricting to patients with an index date on or after March 16, 2022, when both molnupiravir and nirmatrelvir–ritonavir were available); excluding those with negative RT-qPCR results (ie, Ct values imputed with the value of 40) for the first measurement; applying propensity-score adjustment to control for residual confounding bias; and excluding control patients who were not eligible to receive oral antivirals (ie, drug contraindications to nirmatrelvir–ritonavir, severe renal impairment, or severe liver impairment). Additionally, we calculated the absolute risk differences in clinical outcomes between patients with and without viral burden rebound in each group.

All statistical analyses were performed with Stata (version 17). Cubic splines of the logarithmic values were estimated with the Stata command mkspline with knots every 3 days. The mixed-effects restricted cubic spline regression was fitted with the mixed command in Stata with fixed effects for restricted cubic splines and random effects for individuals. All significance tests were two-tailed, with a p value of less than 0·05 considered to indicate statistical significance.

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

Between Feb 26 and June 26, 2022, we identified 40 908 hospitalised patients with a confirmed diagnosis of

	Molnupiravir (n=563)	Nirmatrelvir–ritonavir (n=242)	Control (n=3787)	p value
Age, years	80·7 (12·5)	78·2 (14·2)	78·7 (14·6)	0·0058
18–65	69 (12·3%)	34 (14·1%)	564 (14·9%)	..
>65	494 (87·7%)	208 (86·0%)	3223 (85·1%)	0·25
Sex				
Female	247 (43·9%)	104 (43·0%)	1647 (43·5%)	..
Male	316 (56·1%)	138 (57·0%)	2140 (56·5%)	0·97
Charlson Comorbidity Index	6·0 (2·0)	5·4 (1·8)	5·8 (2·1)	0·0004
0–6	351 (62·3%)	183 (75·6%)	2537 (67·0%)	0·0012
7–15	212 (37·7%)	59 (24·4%)	1250 (33·0%)	..
Imported cases	0	1 (0·4%)	1 (<0·1%)	NA
Immunocompromised*	73 (13·0%)	35 (14·5%)	401 (10·6%)	0·057
Fully vaccinated†	5 (0·9%)	11 (4·5%)	145 (3·8%)	0·0038
Concomitant treatments initiated on the day of admission				
Remdesivir	18 (3·2%)	20 (8·3%)	345 (9·1%)	<0·0001
Antibiotics	485 (86·1%)	192 (79·3%)	3247 (85·7%)	0·022
Immunomodulators	225 (40·0%)	99 (40·9%)	1956 (51·7%)	<0·0001
Dexamethasone	113 (20·1%)	59 (24·4%)	1326 (35·0%)	<0·0001
Other systemic steroid	145 (25·8%)	58 (24·0%)	1061 (28·0%)	0·24
Interferon-β-1b	6 (1·1%)	9 (3·7%)	75 (2·0%)	0·051
Baricitinib	1 (0·2%)	7 (2·9%)	15 (0·4%)	<0·0001
Tocilizumab	0	0	7 (0·2%)	NA
Cycle threshold value on admission, number of cycles	21·8 (6·1)	23·3 (6·9)	23·3 (6·8)	<0·0001
<20	268 (47·6%)	93 (38·4%)	1548 (40·9%)	..
20 to <30	227 (40·3%)	99 (40·9%)	1495 (39·5%)	..
30 to <35	43 (7·6%)	32 (13·2%)	461 (12·2%)	..
≥35	25 (4·4%)	18 (7·4%)	283 (7·5%)	0·00016

Data are n (%) or mean (SD). NA=not applicable. *Immunocompromised patients included those with primary immunodeficiency or on active immunosuppressive treatment at baseline or in the past 12 months. †Fully vaccinated status was defined as having received at least two doses of BNT162b2 or three doses of CoronaVac, and being at least 14 days since the last dose at baseline or the index date.[22]

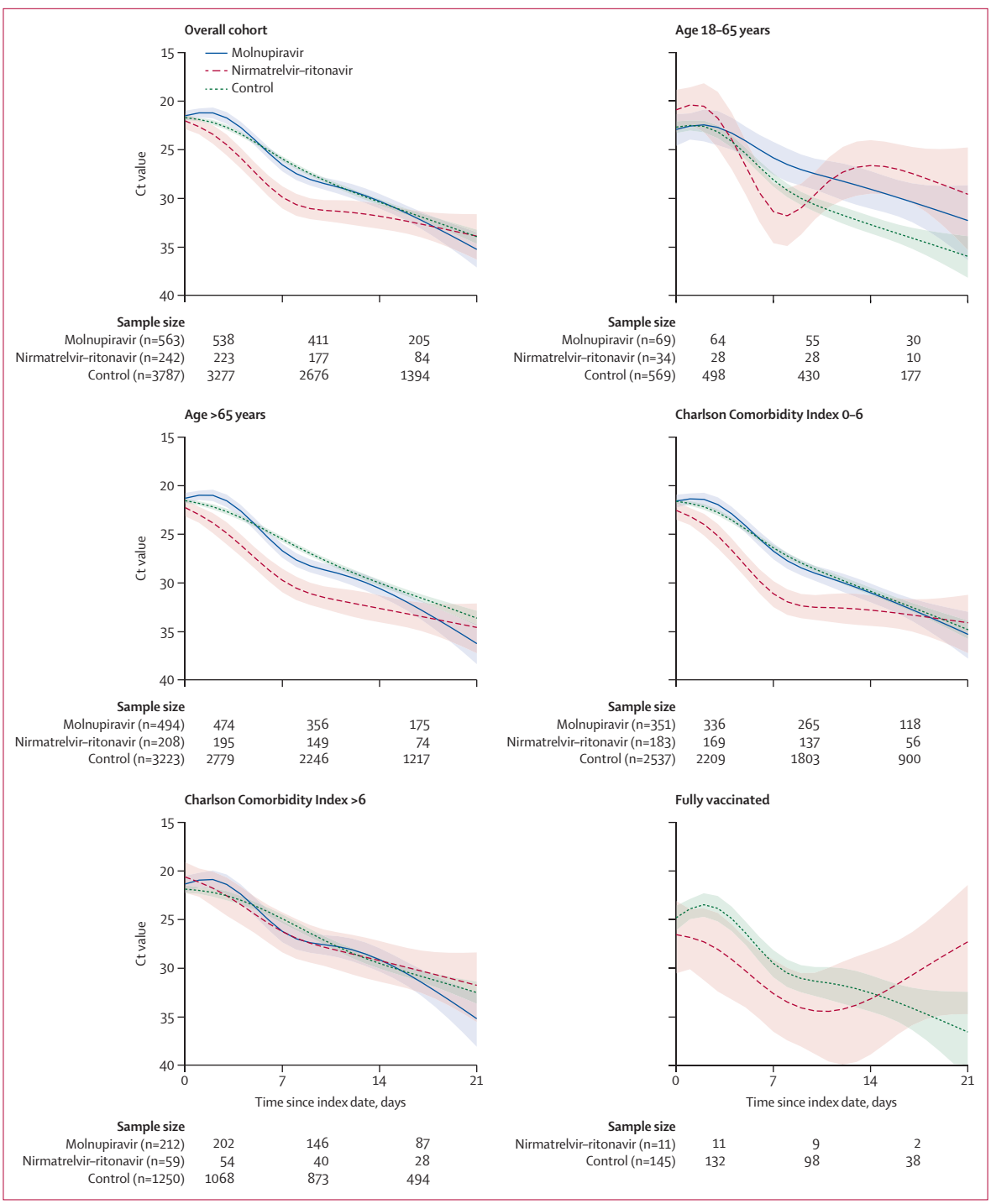
Table 1: **Baseline characteristics of hospitalised patients with COVID-19 in the molnupiravir, nirmatrelvir–ritonavir, and control groups**

COVID-19. After screening for eligibility, 4592 patients who did not initially require supplemental oxygen were included in our retrospective cohort and were observed from Feb 26 to July 3, 2022 (figure 1). Of the 4592 patients, 563 (12·3%) received molnupiravir, 242 (5·3%) received nirmatrelvir–ritonavir, and 3787 (82·5%) did not receive oral antiviral treatment (control group). Baseline characteristics of the study groups are presented in table 1. The cohort comprised 1998 (43·5%) women and 2594 (56·5%) men. The 5-day antiviral regimen was completed by 240 (99·2%) of the 242 patients receiving nirmatrelvir–ritonavir and 535 (95·0%) of the 563 patients receiving molnupiravir. Median duration from the index date to peak viral load was 0 days (IQR 0–3) for patients taking nirmatrelvir–ritonavir, 1 day (0–3) for patients taking molnupiravir, and 1 day (0–6) for control patients. Median times from the index date to two subsequent Ct measurement tests (measurement 2 and measurement 3) were 10 days (8–17) and 15 days (10–21) for patients taking nirmatrelvir–ritonavir, 10 days (8–15) and 13 days (11–18) for patients taking molnupiravir, and 10 days (8–16) and 14 days (10–20) for control patients. Median time to achieve a Ct value above 30 (ie, low viral burden[20]) was 8 days (3–14) for the nirmatrelvir–ritonavir group, 11 days (7–17) for the molnupiravir group, and 10 days (4–17) for the control group. Median time from the index date to initiation of antiviral therapy was 1 day (0–3) for the nirmatrelvir–ritonavir group and 1 day (1–3) for the molnupiravir group.

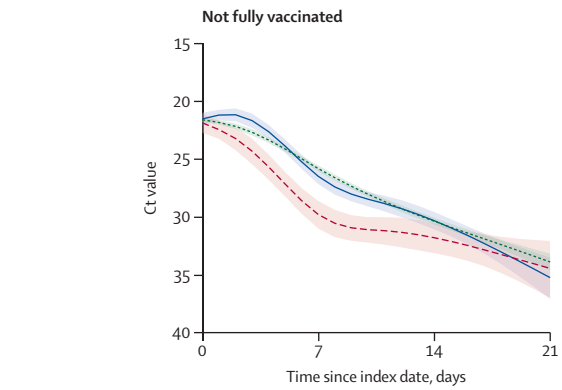
We assessed trajectories of viral burden, proxied by predicted Ct value from serial RT-qPCR measurements over the first 21 days of the disease course (figure 2). In the overall cohort, curves for the molnupiravir and control groups were similar, whereas the nirmatrelvir–ritonavir group showed earlier and quicker reduction in viral burden. Viral burden rebound was not apparent in any of the groups (figure 2; appendix 2 pp 9–10). However, on stratified analysis, viral burden rebound or plateauing of the decline in viral burden was discernible in the nirmatrelvir–ritonavir group in individuals at low risk of progression to severe COVID-19 at baseline (those aged 18–65 years, those with CCI 0–6, or those who were fully vaccinated), within 1–4 days of completion of the 5-day course of antiviral therapy. Viral burden rebound was not observed in individuals in the nirmatrelvir–ritonavir group at high risk of severe COVID-19 at baseline (age >65 years, CCI >6, or not fully vaccinated). Both the molnupiravir and control groups showed no viral rebound when stratified by risk factors. The changes in daily Ct value over the first 21 days of observation had no marked differences between those with early or more frequent Ct value measurements compared with those with later or less frequent testing (appendix 2 pp 4–6).

Viral burden rebound occurred in 16 of 242 patients (6·6% [95% CI 4·1–10·5]) receiving nirmatrelvir–ritonavir, 27 of 563 (4·8% [3·3–6·9]) receiving molnupiravir, and 170 of 3787 (4·5% [3·9–5·2]) in the control group (table 2; appendix 2 p 7). In a post-hoc logistic regression adjusting for potential baseline confounders, we observed no significant difference in the incidence of viral burden rebound across the three groups (appendix 2 p 11). Immunocompromised status was associated with increased odds of viral burden rebound across the groups (nirmatrelvir–ritonavir: OR 7·37 [95% CI 2·56–21·26], p=0·0002; molnupiravir: 3·05 [1·28–7·25], p=0·012; control: 2·21 [1·50–3·27], p<0·0001). Among patients taking nirmatrelvir–ritonavir, the odds of viral burden rebound were higher in those aged 18–65 years (*vs* >65 years; 3·09 [1·00–9·53], p=0·050), those with high comorbidity burden (6·02 [2·09–17·38], p=0·0009), and those concomitantly taking corticosteroids (7·51 [1·67–33·82], p=0·0086), whereas the odds were lower in those who had not been fully vaccinated (0·16 [0·04–0·67], p=0·012). In patients taking molnupiravir, those aged 18–65 years (2·68 [1·09–6·58], p=0·032) or receiving concomitant corticosteroids (3·11 [1·23–7·82], p=0·016) had increased odds of viral burden rebound.

During the period from day 5 of follow-up to the end of follow-up, 106 (18·8%) of 563 patients died in the molnupiravir group, 33 (13·6%) of 242 patients died in the nirmatrelvir–ritonavir group, and 1029 (27·2%) of 3787 died in the control group. We found no association between viral burden rebound and the odds of the composite outcome from day 5 onwards (nirmatrelvir–ritonavir: adjusted OR 1·90 [95% CI 0·48–7·59], p=0·36; molnupiravir: 1·05 [0·39–2·84], p=0·92; control: 1·27 [0·89–1·80], p=0·18; table 3). Additionally, when individual components of the composite outcome were analysed, viral burden rebound was not associated with the



(Figure 2 continues on next page)



Sample size			
Molnupiravir (n=558)	533	408	205
Nirmatrelvir–ritonavir (n=231)	212	168	82
Control (n=3642)	3145	2578	1356

Figure 2: **Changes in Ct value up to 21 days after the index date in the molnupiravir, nirmatrelvir–ritonavir, and control groups**
The index date (day 0) was defined as the date of first symptom onset, first positive quantitative RT-PCR or rapid antigen test, or initiation of molnupiravir or nirmatrelvir–ritonavir, whichever was the earliest. Curves were generated from generalised-additive mixed-effects models and show mean predicted daily Ct values with time for the fixed portion of the models. Shaded areas show the bootstrap 95% CIs of the Ct values from 1000 bootstrap samples. Sample sizes refer to the number of patients with at least one measurement during the respective 7-day intervals (0–6, 7–13, and 14–21 days) since the index date. Ct=cycle threshold.

odds of mortality. Similarly, viral burden rebound was not associated with the odds of ICU admission or invasive mechanical ventilation. The absolute risk differences in clinical outcomes between those with and without viral burden rebound are reported in appendix 2 (pp 12–13). Results of the case-control design and other sensitivity analyses were broadly consistent with those of the main analysis, indicating no association between viral burden rebound and clinical outcomes (appendix 2 pp 14–23). When comparing patients with and without repeated RT-qPCR measurements, we observed some significant differences in baseline covariables of hospitalised patients, notably age, CCI, and initiation of concomitant treatments (appendix 2 pp 24–25). The observed differences suggest that patients with repeated RT-qPCR measurements were likely to have been at higher risk of progression to severe disease at baseline (ie, older age, higher CCI score, and more frequent use of concomitant treatments) than those without repeated measurements.

Discussion

Viral burden rebound was observed in 4–7% of hospitalised patients with non-oxygen-dependent COVID-19 during a pandemic wave dominated by the omicron BA.2.2 variant. This incidence is consistent with previous studies conducted during the peaks of omicron[32] and delta (B.1.617.2)[33] circulation. Furthermore, viral burden rebound appeared to occur among specific patient subgroups (ie, individuals at low baseline risk—including younger adults [age 18–65 years] and those who had been fully vaccinated—and patients in poor prior health including those who were immunocompromised and those taking corticosteroids). Importantly, viral burden rebound was not associated with adverse clinical outcomes.

In a study that assessed viral load rebound in non-hospitalised COVID-19 patients enrolled in the EPIC-HR trial, present or persistent viral load rebound was reported in 17 (1·7%) of 980 patients taking placebo and 23 (2·3%) of 990 patients taking nirmatrelvir–ritonavir, when considering viral load rebound as at least a half log increase in viral load at day 10 and day 14 of follow-up relative to day 5 (end of treatment).[33] In addition to observing viral load rebound in both treatment groups, the occurrence of hospitalisation or death and baseline serostatus were similar between the groups; and the study suggested that viral load rebound was unlikely to be associated with a relapse of moderate-to-severe symptoms, low nirmatrelvir exposure, or treatment-emergent mutations at the M^{pro} gene or corresponding viral cleavage sites.[33] Notably, the EPIC-HR trial was conducted among unvaccinated patients infected with the delta variant. In the past year, cases of symptom recurrence or re-positive viral test after a brief recovery have mostly been described in patients taking nirmatrelvir–ritonavir who were fully vaccinated or even boosted, and with breakthrough infections of the omicron variant.[33]

Various mechanisms have been proposed to explain COVID-19 rebound. Firstly, researchers have argued that it might represent a natural course of SARS-CoV-2 infection,[11,15,17,33] involving a biphasic pattern of decrease in viral load after the peak that corresponds to different stages of innate and acquired immune responses,[34–37] and intermittent viral shedding.[38–41] Secondly, the dosage, duration, and timing of nirmatrelvir–ritonavir initiation might affect COVID-19 rebound. For instance, drug exposure might be insufficient for adequate viral clearance in some patients considering individual pharmacokinetics, comorbidities, or interactions with

	Molnupiravir (n=563)			Nirmatrelvir–ritonavir (n=242)			Control (n=3787)		
	Patients with viral burden rebound, n/N (%)	OR (95% CI)	p value	Patients with viral burden rebound, n/N (%)	OR (95% CI)	p value	Patients with viral burden rebound, n/N (%)	OR (95% CI)	p value
Overall	27/563 (4·8%)	..	..	16/242 (6·6%)	..	..	170/3787 (4·5%)	..	..
Age, years									
18–65	7/69 (10·1%)	2·68 (1·09–6·58)	0·032	5/34 (14·7%)	3·09 (1·00–9·53)	0·050	28/564 (5·0%)	1·13 (0·75–1·72)	0·55
>65	20/494 (4·0%)	1 (ref)	..	11/208 (5·3%)	1 (ref)	..	142/3223 (4·4%)	1 (ref)	..
Sex									
Male	18/316 (5·7%)	1·60 (0·70–3·62)	0·26	10/138 (7·2%)	1·28 (0·45–3·63)	0·65	100/2140 (4·7%)	1·10 (0·81–1·51)	0·53
Female	9/247 (3·6%)	1 (ref)	..	6/104 (5·8%)	1 (ref)	..	70/1647 (4·3%)	1 (ref)	..
Charlson Comorbidity Index									
0–6	15/351 (4·3%)	1 (ref)	..	6/183 (3·3%)	1 (ref)	..	108/2537 (4·3%)	1 (ref)	..
>6	12/212 (5·7%)	1·34 (0·62–2·93)	0·46	10/59 (16·9%)	6·02 (2·09–17·38)	0·0009	62/1250 (5·0%)	1·17 (0·85–1·62)	0·33
Vaccination status									
Fully vaccinated†	0/5	1 (ref)	..	3/11 (27·3%)	1 (ref)	..	8/145 (5·5%)	1 (ref)	..
Not fully vaccinated	27/558 (4·8%)	NA	NA	13/231 (5·6%)	0·16 (0·04–0·67)	0·012	162/3642 (4·4%)	0·80 (0·38–1·65)	0·54
Concomitant corticosteroid use									
Yes	21/305 (6·9%)	3·11 (1·23–7·82)	0·016	14/123 (11·4%)	7·51 (1·67–33·82)	0·0086	123/2515 (4·9%)	1·34 (0·95–1·89)	0·094
No	6/258 (2·3%)	1 (ref)	..	2/119 (1·7%)	1 (ref)	..	47/1272 (3·7%)	1 (ref)	..
Immunocompromised‡									
Yes	8/73 (11·0%)	3·05 (1·28–7·25)	0·012	8/35 (22·9%)	7·37 (2·56–21·26)	0·0002	34/401 (8·5%)	2·21 (1·50–3·27)	<0·0001
No	19/490 (3·9%)	1 (ref)	..	8/207 (3·9%)	1 (ref)	..	136/3386 (4·0%)	1 (ref)	..

OR=odds ratio. NA=not applicable. Ct=cycle threshold. *Defined as a reduction in Ct value between two consecutive measurements larger than or equal to 3, with this decrease sustained in at least the immediately subsequent Ct measurement for those patients with three or more Ct measurements ($\Delta Ct=Ct_{[measurement\ 1]}-Ct_{[measurement\ 2]}\geq 3$ and $\Delta Ct=Ct_{[measurement\ 1]}-Ct_{[measurement\ 3]}\geq 3$). †Fully vaccinated status was defined as having at least two doses of BNT162b2 or three doses of CoronaVac, and being at least 14 days since the last dose at baseline or the index date.[22] ‡Immunocompromised patients included those with primary immunodeficiency or on active immunosuppressive treatment at baseline or in the past 12 months.

Table 2: **Identification of risk factors associated with viral burden rebound***

	Molnupiravir (n=563)			Nirmatrelvir–ritonavir (n=242)			Control (n=3787)		
	Patients, n/N*	% or OR (95% CI)	p value	Patients, n/N*	% or OR (95% CI)	p value	Patients, n/N*	% or OR (95% CI)	p value
Composite outcome†	112/558	20·1% (16·7–23·4)	NA	36/240	15·0% (10·5–19·5)	NA	1103/3736	29·5% (28·1–31·0)	NA
With viral burden rebound	6/27	22·2% (5·5–39·0)	..	8/15	53·3% (24·7–81·9)	..	61/167	36·5% (29·1–43·9)	..
Without viral burden rebound	106/531	20·0% (16·6–23·4)	..	28/225	12·4% (8·1–16·8)	..	1042/3569	29·2% (27·7–30·7)	..
Adjusted OR	..	1·05 (0·39–2·84)	0·92	..	1·90 (0·48–7·59)	0·36	..	1·27 (0·89–1·80)	0·18
Mortality	106/563	18·8% (15·6–22·1)	NA	33/242	13·6% (9·3–18·0)	NA	1029/3787	27·2% (25·8–28·6)	NA
With viral burden rebound	5/27	18·5% (2·9–34·2)	..	8/16	50·0% (22·5–77·5)	..	55/170	32·4% (25·2–39·5)	..
Without viral burden rebound	101/536	18·8% (15·5–22·2)	..	25/226	11·1% (6·9–15·2)	..	974/3617	26·9% (25·5–28·4)	..
Adjusted OR	..	0·88 (0·30–2·55)	0·81	..	2·62 (0·67–10·25)	0·17	..	1·18 (0·82–1·69)	0·37
ICU admission or invasive mechanical ventilation initiation	11/558	2·0% (0·8–3·1)	NA	8/240	3·3% (1·0–5·6)	NA	190/3736	5·1% (4·4–5·8)	NA
With viral burden rebound	1/27	3·7% (0·0–11·3)	..	3/15	20·0% (0·0–42·9)	..	12/167	7·2% (3·2–11·1)	..
Without viral burden rebound	10/531	1·9% (0·7–3·0)	..	5/225	2·2% (0·3–4·2)	..	178/3569	5·0% (4·3–5·7)	..
Adjusted OR	..	2·67 (0·29–24·22)	0·38	..	3·35 (0·35–32·49)	0·30	..	1·25 (0·66–2·35)	0·49

The baseline covariables of age, sex, pre-existing morbidities, vaccination status, concomitant treatments initiated, and Ct value on admission were considered in the adjusted regression model. OR=odds ratio. NA=not applicable. ICU-intensive care unit. *Patients with the outcome during the first 4 days from the index date were excluded from the analysis. †Composite outcome includes mortality, ICU admission, and initiation of invasive mechanical ventilation.

Table 3: **Associations between viral burden rebound and study outcomes**

concomitant medications.[13,18,42] Additionally, the duration of therapy could be too short for specific patients, such as those who are immunocompromised, as host immune responses might not be mounted adequately after the antiviral is discontinued.[16,42] Similarly, another postulation is that nirmatrelvir–ritonavir therapy might be initiated too early during the course of disease for some cases, at which point the inhibition of viral replication could be transient, and viral activity could resume while the host immune responses are maturing, allowing for virological

rebound and symptom recurrence.[16,17,42,43] Modelling studies of SARS-CoV-2 infection have suggested that the potency, timing, and duration of antiviral treatments are likely to influence viral dynamics, with an extremely early initiation (eg, immediately after symptom onset) of a short-term therapy potentially prolonging viral shedding, or even leading to post-treatment rebound from incomplete viral suppression during the treatment course.[34,35,39] In our cohort, viral burden rebound was observed in both groups receiving oral antivirals. Molnupiravir inhibits viral replication by inducing mutagenesis during viral RNA synthesis, which is probably irreversible, whereas nirmatrelvir inhibits replication by reversible inhibition of M^{pro}, and the viral enzyme could restore its function if it is not completely inhibited or once the drug is discontinued.[44,45] Thus, the possibility of viral rebound is higher with nirmatrelvir treatment while the host immune responses are still maturing. Thirdly, *M*^{pro} mutations that are potentially resistant to nirmatrelvir could occur naturally;[46,47] however, current evidence does not generally support a treatment-emergent mutation as being responsible for viral rebound in patients receiving nirmatrelvir–ritonavir, nor does it support SARS-CoV-2 reinfection of a different strain.[11,14,33,42] Lastly, while some researchers have recognised the role of immune factors in viral rebound, recent studies have confirmed that immune responses are likely to be intact in immunocompetent patients who have experienced symptom recurrence or re-positive viral tests after nirmatrelvir–ritonavir treatment, as shown by the presence of both neutralising antibodies and T-cell responses in adaptive immunity.[13,14,16]

Regarding risk predictors for viral burden rebound, we observed increased odds of rebound in patients who were immunocompromised or receiving concomitant corticosteroids in our study. This finding is generally in accordance with empirical evidence suggesting that viral rebound was more likely to occur in patients receiving immunosuppressants and organ transplants, than in those without these factors.[18] Additionally, among seven patients with viral rebound, culturable virus was isolated from the patients who had underlying immune suppression.[16] Consistent with a preprint study by Wang and colleagues,[18] patients with COVID-19 rebound after oral antiviral treatment in our cohort had more pre-existing comorbidities than those without COVID-19 rebound; however, further research is needed to delineate the relationship between comorbidities and age among patients with and without rebound. Interestingly, patients with COVID-19 rebound after oral antiviral treatment in the previous study also had higher vaccination rates than those without,[18] which was evident in our nirmatrelvir–ritonavir cohort. In a small prospective observational study of fully vaccinated or boosted individuals with breakthrough SARS-CoV-2 infections of the omicron BA.2 lineage, three (27·3%) of 11 patients treated with nirmatrelvir–ritonavir had viral rebound (at least two Ct values ≥35 followed by at least two Ct values <35),[48] which is the same proportion as in our nirmatrelvir–ritonavir cohort who had been fully vaccinated and experienced viral burden rebound (three [27·3%] of 11). These findings raise the possibility of vaccine-induced immune imprinting, in which breakthrough natural infection might recall vaccine-induced memory responses among vaccinated individuals. Such immune imprinting to the ancestral strain of SARS-CoV-2 as elicited by COVID-19 vaccines could potentially render the development of immune responses, especially neutralising antibodies, against variant strains less effective.[49] This effect might be particularly relevant for breakthrough infections with the omicron variant in boosted individuals, given that both cross-reactive humoral and adaptive immunity could be less potent against this variant of concern compared with previous variants of concern.[50] Even among COVID-19 patients who were not receiving oral antivirals, a cohort study by Hay and colleagues[32] identified a higher rate of viral rebound in boosted individuals compared with two-dose vaccinated or unvaccinated individuals. Although an increased rate of viral clearance has been recognised with vaccination and breakthrough infections,[51] further studies are needed to explore the mechanisms of COVID-19 rebound in individuals who have been fully vaccinated or boosted. Ideally, future studies should measure patient immune responses, to test whether vaccine-induced immune imprinting has a role in limiting immune activity against the omicron variant, and thus predisposes patients to virological rebound after the completion of antiviral treatment, taking into account patient serological status and time since last vaccine dose.[17]

Our study has several limitations. Firstly, although Ct values can be considered a proxy of viral burden in patients with COVID-19, we did not have access to information on the omicron subvariants causing infection, the corresponding standard curve for quantification of viral load, or viral culture results to complement the observation of viral RNA shedding. In addition, the prognostic consequences of viral burden rebound have not yet been determined. Nevertheless, during our observation period, 98·4% of SARS-CoV-2 infections were by the omicron BA.2.2 subvariant in Hong Kong.[19] The absence of SARS-CoV-2 sequencing data also prevents us from excluding the possibility of treatment-resistant mutations, or differentiating between relapse or re-positivity versus reinfection, although reinfection occurring within such a short period of time would be rare. Secondly, during the study period, when the public health-care system was overwhelmed with COVID-19 cases, Ct measurements might not have been performed regularly, since a particular Ct value cutoff was no longer adopted as one of the criteria for discharge.[52] Nonetheless, we excluded patients with missing Ct values before or during antiviral treatment and after antiviral

treatment, and control patients with missing Ct values after 5 days of the first measurement, to ensure that serial measurements could be obtained for the identification of viral rebound. With the understanding that early or more frequent RT-qPCR tests could increase the likelihood of viral rebound detection, we did a further analysis of surveillance bias; this had minimal effect on the base case results. We did observe that patients with repeated RT-qPCR measurements (included in this study) were likely to have been at higher risk of progression to severe disease at baseline than those without repeated measurements (excluded from the analyses); thus, potential selection bias cannot be ruled out. Thirdly, data on detailed clinical symptoms, or rapid antigen test results after the index date, were not available, nor were data on immune responses or serostatus in patients with and without viral rebound. Fourthly, data availability meant that the only internally valid sampling frame was among hospitalised patients. Therefore, the generalisability of our results might be restricted to the inpatient setting and characteristics of the included patients (ie, mostly older patients who had not been fully vaccinated). Finally, although we attempted to explore the associations between patient characteristics and viral burden rebound, the interpretation of our results is likely to be limited by the small sample sizes of patient subgroups, and further work is required to precisely estimate the risk of rebound in relation to individual comorbidities and clinical conditions. Indeed, the preprint study by Wang and colleagues suggested some patient characteristics associated with viral rebound versus no rebound among patients taking oral antivirals.[18] Furthermore, various research questions are yet to be addressed, including a standard definition of COVID-19 rebound, whether a correlation exists between symptom recurrence and virological rebound, the nature and frequency of rebound occurrence in different patient populations, potential mechanisms of rebound, and the effect of antiviral therapy (dosage, duration, and timing) on rebound. Although not statistically significant, the apparent over-representation of patients with viral burden rebound who met the clinical outcomes of mortality, intensive care unit admission, or invasive mechanical ventilation initiation in the nirmatrelvir–ritonavir group, compared with the molnupiravir and control groups, should be verified by future studies.

Based on observations in this population-wide retrospective cohort of hospitalised COVID-19 patients, we conclude that viral burden rebound was not a common event, and was observed with or without oral antiviral use. Increased odds of rebound were apparent in specific patient subgroups. Viral burden rebound did not appear to be associated with adverse serious clinical outcomes, and thus oral antivirals should continue to be offered to COVID-19 patients at risk of severe or fatal outcomes. Further research is needed to establish a standard definition of COVID-19 rebound for comparison across studies, and to identify the underlying mechanism, and possible variation by timing, dosage, and duration of antiviral therapy.

Contributors

The study was designed by CKHW, GML, and BJC. All authors had access to the underlying data in the study. The underlying data were accessed and verified by CKHW, ICHA, and EHYL. Data were analysed by CKHW and ICHA. CKHW and KTKL wrote the first draft of the manuscript which was revised by IFNH, LLMP, GML, and BJC. All authors interpreted data, provided critical review and revision of the text, and approved the final version of the manuscript, and were responsible for the decision to submit for publication.

Declaration of interests

CKHW reports receipt of research funding from the EuroQoL Group Research Foundation, AstraZeneca, and Boehringer Ingelheim, unrelated to this work. BJC reports honoraria from AstraZeneca, Fosun Pharma, GlaxoSmithKline, Moderna, Pfizer, Roche, and Sanofi Pasteur. BJC has provided scientific advice to Pfizer and AstraZeneca on issues related to disease burden and vaccine effectiveness; BJC has not provided scientific advice to Pfizer or AstraZeneca related to COVID-19 antiviral effectiveness, and has not received any funding from Pfizer or AstraZeneca for any research on antiviral effectiveness including the current work. IFNH has received speaker honoraria from MSD and was an advisory board member for Pfizer, Gilead, Fosun, MSD, and AstraZeneca. All other authors declare no competing interests.

Data sharing

The clinical outcome data and vaccination records were extracted from the Hospital Authority database in Hong Kong and data on confirmed cases of SARS-CoV-2 infection were extracted from the eSARS data provided by the Centre for Health Protection (Department of Health, The Government of the Hong Kong Special Administrative Region). The data custodians (the Hospital Authority and the Department of Health) provided the underlying individual patient data to The University of Hong Kong for the purpose of performing scientific research for the study. Restrictions apply to the availability of these data, which were used under licence of the Hospital Authority and the Department of Health for this study. The authors cannot transmit or release the data, in whole or in part in whatever form or media, or to any other parties or place outside Hong Kong; and the authors fully comply with the duties under the laws of Hong Kong relating to the protection of personal data including those under the Personal Data (Privacy) Ordinance and its principles in all aspects.

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