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ORIGINAL ARTICLE

Risk of acute liver injury following the nirmatrelvir/ritonavir use

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Abstract

Background: Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported as adverse events of nirmatrelvir/ritonavir users in the EPIC-HR trial.

Aim: To quantify the risk and severity of acute liver injury (ALI) associated with nirmatrelvir/ritonavir use.

Methods: This self-controlled case-series study was conducted using electronic medical records of patients with confirmed diagnosis of SARS-CoV-2 infection between 26th February 2022 and 12th February 2023 in Hong Kong.

Results: Among 2 409 848 patients with SARS-CoV-2 infection during the study period, 153 853 were prescribed with nirmatrelvir/ritonavir, of whom 834 (.5%) had incident ALI (moderate: 30.5%; moderate to severe: 18.9%; severe or fatal: 5.8%). Compared with the non-exposure period, risk of ALI increased significantly during the pre-exposure period (IRR = 38.13, 95% CI = 29.29–49.62) and remained elevated during the five-day nirmatrelvir/ritonavir treatment (IRR = 20.75, 95% CI = 17.06–25.25) and during wash-out period (IRR = 16.27, 95% CI = 13.23–20.01). Compared to the pre-exposure period, risk of ALI was not increased during the five-day nirmatrelvir/ritonavir treatment period (IRR = .54, 95% CI = .43–.70). Compared to 5469 non-nirmatrelvir/ritonavir users with incident ALI, nirmatrelvir/ritonavir users had less severe ALI by the severity index ($p < .001$) and peak INR (1.7 vs. 2.3; $p < .001$). ALI cases with nirmatrelvir/ritonavir use had lower risk of all-cause death (29.1% vs. 39.1%; OR = .64; $p < .001$) and no increase in risk of liver decompensation (1.0% vs. 1.3%; OR = .62; $p = .230$) compared to non-users.

Conclusion: The risk of ALI associated with nirmatrelvir/ritonavir treatment for COVID-19 was elevated in the pre-exposure period, but not following nirmatrelvir/ritonavir initiation. ALI following nirmatrelvir/ritonavir treatment were mostly mild and less severe than ALI events in non-nirmatrelvir/ritonavir users.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACEI, angiotensin converting enzyme inhibitor; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; CIs, confidence intervals; COVID-19, coronavirus disease 2019; CYP3A, cytochrome P450 3A; DILI, drug-induced liver injury; DILIN, Drug-induced Liver Injury Network; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; IRRs, incidence rate ratios; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; RAT, rapid antigen test; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SCCS, self-controlled case series; SD, standard deviations; ULN, upper limit of normal.

Carlos King Ho Wong, Lung Yi Mak, and Ivan Chi Ho Au contributed equally to this work.

KEYWORDS
acute liver injury, case series, COVID-19, nirmatrelvir/ritonavir

1 | INTRODUCTION

Ritonavir-boosted nirmatrelvir (nirmatrelvir/ritonavir) is one of the first-line antiviral therapies for treatment of infection due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). Liver injury may occur when administering nirmatrelvir/ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis, as stated in the product label[1,2]; and presents with hepatic transaminase elevations, clinical hepatitis and jaundice especially among patients receiving ritonavir.[1] The EPIC-HR trial (Phase 2–3) showed 1.5% of nirmatrelvir/ritonavir users experienced elevated alanine (ALT).[3] On the other hand, a study with similar population and slight overlapping time frame as our study showed minimal risk of drug-induced liver injury (DILI) with molnupiravir and nirmatrelvir/ritonavir.[4] Therefore, whether nirmatrelvir/ritonavir causes significant liver injury remains debatable. To complicate the matter, serum aminotransferase elevations are seen in up to 70% of patients with symptomatic SARS-CoV-2 infection and tend to correlate with disease severity.[5,6] Meanwhile, the pharmacodynamic characteristics of nirmatrelvir and ritonavir do not refute the possibility of direct hepatotoxicity. Nirmatrelvir is metabolized by cytochrome P450 3A (CYP3A) which is inhibited by ritonavir, leading to persistently high serum concentration of nirmatrelvir and resultant heightened risk of liver damage.

Ritonavir, the protease inhibitor, is associated with several metabolic abnormalities, including drug-induced steatosis, which is mainly caused by drug interference with β-oxidation of fatty acids and/or mitochondrial respiration, causing the accumulation of non-esterified fatty acids which are converted into triglycerides.[7,8] In a previous study by Griffin et al., 10-minute exposure of rat hepatocytes to ritonavir caused intracellular accumulation of taurocholic acid; thus, hepatotoxicity induced by ritonavir may be due to interference with bile acids efflux from liver cells.[9] In another recent study, hepatotoxicity of ritonavir interfered with ER-Golgi trafficking via inhibiting Ras converting CAAX endopeptidase-1 and its potential substrates, subsequently promoting cellular stress responses and fatty liver disease.[10] Also, ritonavir can potentially reactivate hepatitis B and C viral infections, and hence deterioration of the liver disease.[8]

The aim of this study is to investigate whether nirmatrelvir/ritonavir is associated with an increased risk of liver injury in the real-world setting. The study objective is to compare the risk of acute liver injury (ALI) prior to and after nirmatrelvir/ritonavir initiation among COVID-19 patients excluding those who had incident ALI prior to SARS-CoV-2 infection.

Key points

Nirmatrelvir/ritonavir treatment did not increase the risk of acute liver injury (ALI). ALI following nirmatrelvir/ritonavir treatment were mostly mild and less severe than ALI events in non-nirmatrelvir/ritonavir users.

2 | PATIENTS AND METHODS

2.1 | Data source, study population and design

We analysed patients with confirmed diagnosis of SARS-CoV-2 infection, defined by positive rapid antigen test (RAT) and/or polymerase chain reaction (PCR) test results, in the Hong Kong Special Administrative Region, China for the study period between 26th February 2022 (the date when oral antivirals were available for use in Hong Kong) and 12th February 2023 using self-controlled case series (SCCS) method. Patients with a liver injury that met the outcome criteria 180 days before the SARS-CoV-2 infection were excluded from the analysis. Electronic medical records of patients with COVID-19 were retrieved from the Hong Kong Hospital Authority, a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong, with data linkage to vaccination records from Department of Health.[11] The linked database was used to investigate the effectiveness of COVID-19 vaccination and drug treatment.[11-14]

Nirmatrelvir/ritonavir was locally available for prescription from 16th March 2022. Based on the Hospital Authority clinical management guidelines for COVID-19,[15] patients who had mild symptoms, were at risk of progression to severe disease, and at an early stage of COVID-19 (within 5 days of symptom onset) were recommended to receive nirmatrelvir/ritonavir (nirmatrelvir 300 mg and ritonavir 100 mg twice daily for 5 days, or nirmatrelvir 150 mg and ritonavir 100 mg twice daily for 5 days if the estimated glomerular filtration rate [eGFR] was 30–59 mL/min/1.73 m^2). Nirmatrelvir/ritonavir was not recommended to those who were on medications with potential drug–drug interactions with nirmatrelvir/ritonavir,[2] severe renal impairment (eGFR <30 mL/min/1.73 m^2), or severe hepatic impairment (Child-Pugh Class C).

2.2 | Outcome definition

ALI was defined as satisfying at least one of the following conditions[6]: (i) increase in ALT greater than five times the upper limit of

normal (ULN); (ii) increase in AST greater than five times the ULN; (iii) increase in total bilirubin greater than five times the ULN; or (iv) the international normalized ratio (INR) over 1.5.[16] According to the Asia Pacific Association of Study of Liver consensus guidelines,[17] the ULN of ALT, AST, and total bilirubin were defined as 40 U/L, 40 U/L,[18] and 19 μmol/L, respectively.

Severity of ALI following nirmatrelvir/ritonavir use was assessed by the peak ALT level, peak AST level, peak total bilirubin, peak INR, and Drug-induced Liver Injury Network (DILIN) scale.[19] In addition, the events following ALI diagnosis were assessed, including the proportion of patients requiring intensive care unit (ICU) admission, mortality, and liver decompensation (namely ascites, hepatic encephalopathy, jaundice, and liver transplantation).

Severe SARS-CoV-2 infection was identified using diagnostic coding during admission: mechanical ventilation, non-invasive positive pressure ventilation, oxygen therapy, hypoxaemia, pneumonia, acute respiratory distress syndrome, septic shock, septicaemia, high C-reactive protein (>50 mg/L), and multi-organ failure, and prescription with corticosteroid (prednisolone, dexamethasone, or hydrocortisone), tocilizumab, or baricitinib during admission. The presence of any of these can be classified as severe SARS-CoV-2 infection.

2.3 | Self-controlled case series (SCCS)

A self-controlled case series (SCCS) design was used to investigate the risk of ALI following nirmatrelvir/ritonavir use. The SCCS was developed for vaccine safety and pharmacovigilance research, and DILI research.[20,21] The SCCS study design relies on comparisons within individuals who have experienced both the outcome and exposure of interest during the observation period, with participants serving as their own control.[22,23] Incidence rate ratios (IRRs) are derived by comparing the rate of events during periods of treatment exposure with the rate during all other observed time periods (i.e., before and after nirmatrelvir/ritonavir use). The major advantage of SCCS lies in its ability to control for all time-invariant confounding that possibly vary between individuals, such as socioeconomic factors and genetic factors.[22]

2.4 | Study assumptions

Three assumptions have to be satisfied to ensure the adequacy of SCCS model and interpretation of results.[23] First, the event occurrence should not change the probability of exposure. We have included a pre-exposure period, defined as the risk period before nirmatrelvir/ritonavir initiation, to address this problem. Secondly, the recurrences of the event should be independent. Otherwise, the incident event may increase the occurrence of future events. Therefore, only the incident ALI episode was included in this study. Lastly, the observation period should not be shortened by the event. Distributions of time from ALI occurrence to end of observation period were compared between the censored and uncensored cases. A large discrepancy in the distribution plot indicates the existence of censoring effect and an extension of the SCCS model would be needed for unbiased estimation.

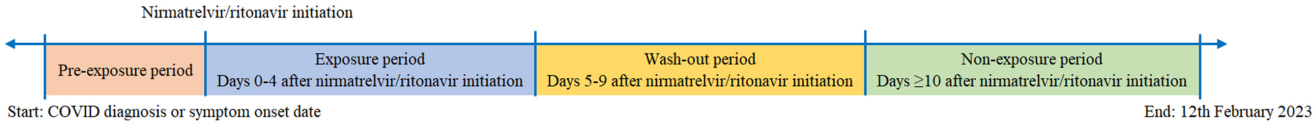
2.5 | Exposure and risk periods

Study exposure was the initiation of nirmatrelvir/ritonavir treatment in patients following SARS-CoV-2 infection diagnosis or symptom onset. Patients were censored on the date of death. The observation period was divided into four mutually exclusive risk windows: (i) the pre-exposure period covering that from SARS-CoV-2 infection diagnosis or symptom onset to 1 day before treatment initiation; and the exposure-related risk periods were defined as (ii) the first 5 days (days 0–4) on nirmatrelvir/ritonavir initiation, (iii) the wash-out period (days 5–9 after treatment initiation); and (iv) the non-exposure period, that is more than 5 days after treatment completion to the end of observation period (days ≥10 after treatment initiation), which would be used as reference for comparison. The pre-exposure period, which was designed to evaluate any increased incidences of ALI before the initiation of nirmatrelvir/ritonavir, would help prevent any temporary changes of probability of exposure.[23] Figure 1 illustrates the schema of SCCS, and describes the four risk periods in this study.

2.6 | Statistical analysis

Characteristics of nirmatrelvir/ritonavir users and non-users who had incident ALI during the observation period were compared. The association between nirmatrelvir/ritonavir use and ALI during different risk periods were estimated by comparing the rates of event occurrence. Number of incident ALI events and person-days of each risk period were calculated. Incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (CIs) of events for different risk periods compared with the non-exposure period were estimated using conditional Poisson regression model with an offset for the length of the risk period. Age is not adjusted for in the analysis given the short observation period. Differences in ALI severity between the users and non-users were compared using ordered or linear regressions adjusting for baseline characteristics.

Subgroup and sensitivity analyses were conducted to assess the robustness of the main results. Subgroups analyses included (1) age ≤ 65 years and age > 65 years, (2) male and female patients, (3) those with severe SARS-CoV-2 infection and those with milder infection, (4) those with and without pre-existing chronic liver disease, (5) those with and without SARS-CoV-2 vaccination, and (6) those with baseline cycle threshold (Ct) value <20 cycles (ie., high viral load) and those with baseline Ct value ≥20 cycles (ie., non-high viral load).[24,25] Sensitivity analyses included (1) standard SCCS without censoring at death, (2) extended SCCS for event-dependent observation period, (3) using 2 × ULN as definition of ALI, (4) using 3 × ULN as definition of ALI, (4) excluding those who did not have



Notes:

Observation period: from COVID-19 diagnosis or symptom onset date (whichever the earliest) to 12th February 2023. Patients were censored on the date of death.

Pre-exposure period: from COVID-19 diagnosis or symptom onset date (whichever the earliest) to the day before nirmatrelvir/ritonavir initiation

FIGURE 1 Observation timeline of patients who received nirmatrelvir/ritonavir in the self-controlled case series. Observation period: from COVID-19 diagnosis or symptom onset date (whichever the earliest) to 12th February 2023. Patients were censored on the date of death. Pre-exposure period: from COVID-19 diagnosis or symptom onset date (whichever the earliest) to the day before nirmatrelvir/ritonavir initiation.

pre-exposure period, (5) restricting non-exposure period to 30 days from nirmatrelvir/ritonavir initiation, (6) including those with at least one measurement of ALT, AST total bilirubin, or INR within days 0–2 from COVID diagnosis or symptom onset, (7) adjusting for antibiotics use as time-varying covariate, (8) adjusting for remdesivir use as time-varying covariate, and (9) adjusting for molnupiravir use as time-varying covariate.

All statistical analyses were performed with the Stata version SE 17.0 (StataCorp LLC) and R, and the R code was adapted in a SCCS approach in this study.[26] A two-sided significance level of 5% was used in all statistical analyses.

2.7 | Ethics approval

This study was approved by the institutional review board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (reference number UW 20–493). Individual patient-informed consent was not required for this retrospective cohort study using anonymised data.

3 | RESULTS

3.1 | Baseline characteristics

Among 2 409 848 patients with confirmed diagnosis of SARS-CoV-2 infection between 26th February 2022 and 12th February 2023, 153 853 of them were prescribed with nirmatrelvir/ritonavir (Figure 2). The baseline characteristics between nirmatrelvir/ritonavir users and non-users are shown in Table S1. As expected, patients prescribed with nirmatrelvir/ritonavir were older, with more medical comorbidities including underlying liver disease, had more severe SARS-CoV-2 infection, and higher viral load, reflecting the adherence to clinical guidelines of antiviral prescription for high-risk groups. There were 834 (.5%) nirmatrelvir/ritonavir users who had incident ALI, and 5469 (.2%) nirmatrelvir/ritonavir non-users who had incident ALI. Incidence rates of ALI among COVID-19 patients

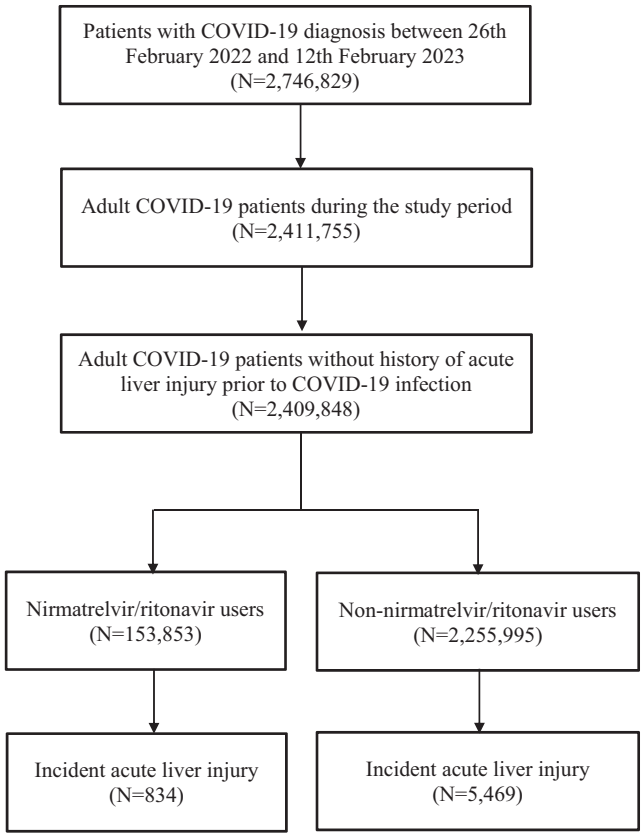


FIGURE 2 Flowchart of inclusion and exclusion of acute liver injury cases of COVID-19 patients with and without nirmatrelvir/ritonavir use between 26th February 2022 and 12th February 2023 in Hong Kong SAR, China.

with and without nirmatrelvir/ritonavir use were 4.70 and 1.18 per 100 000 person-days, respectively. Distributions of timing of nirmatrelvir/ritonavir initiation, and that of incident outcomes by the day since nirmatrelvir/ritonavir initiation are plotted in Figures S1 and S2, respectively. Baseline characteristics of nirmatrelvir/ritonavir users and non-users who had incident ALI are listed in Table 1. The majority of the cohort was aged >65 years old, with presence of medical comorbidities, and use of long-term medications. Chronic

TABLE 1 Characteristics of nirmatrelvir/ritonavir users and non-nirmatrelvir/ritonavir users developing acute liver injury for the first time between 26th February 2022 and 12th February 2023.

	Nirmatrelvir/ritonavir users (*N* = 834)		Non-nirmatrelvir/ritonavir users (*N* = 5469)		
Baseline characteristics	***N*/mean**	**%/SD**	***N*/mean**	**%/SD**	***p*-value[d]**
Age, years[b]	76.1	14.2	74.7	15.3	.015
18–40	24	(2.9%)	212	(3.9%)	.017
40–65	138	(16.6%)	1093	(20.0%)	
>65	672	(80.6%)	4164	(76.1%)	
Sex					
Male	527	(63.2%)	3299	(60.3%)	.114
Female	307	(36.8%)	2170	(39.7%)	
Regions					
Hong Kong Island	262	(31.4%)	791	(14.5%)	<.001
Kowloon	236	(28.3%)	1891	(34.6%)	
New Territories	336	(40.3%)	2773	(50.7%)	
Others	0	(.0%)	14	(.3%)	
Nursing home residents	118	(14.1%)	1279	(23.4%)	<.001
Symptom onset date reported	214	(25.7%)	2231	(40.8%)	<.001
Nosocomial infection	43	(5.2%)	391	(7.1%)	.035
Charlson's index[bc]	5.6	2.0	5.9	2.3	<.001
0–4	219	(26.3%)	1381	(25.3%)	<.001
5–6	373	(44.7%)	2030	(37.1%)	
7–14	242	(29.0%)	2058	(37.6%)	
Diabetes mellitus	333	(39.9%)	2543	(46.5%)	<.001
Hypertension	707	(84.8%)	4726	(86.4%)	.201
Chronic liver disease	92	(11.0%)	559	(10.2%)	.474
Chronic lung disease	182	(21.8%)	1584	(29.0%)	<.001
Chronic heart disease	204	(24.5%)	1781	(32.6%)	<.001
Chronic kidney disease	32	(3.8%)	606	(11.1%)	<.001
Malignancy	127	(15.2%)	571	(10.4%)	<.001
Long-term medications					
ACEI/ARB	346	(41.5%)	2782	(50.9%)	<.001
Anticoagulant	404	(48.4%)	3494	(63.9%)	<.001
Antiplatelet	296	(35.5%)	2255	(41.2%)	.002
Lipid-lowering agent	426	(51.1%)	3047	(55.7%)	.012
NSAID	418	(50.1%)	2826	(51.7%)	.403
Previous SARS-CoV-2 infection	0	(.0%)	2	(.0%)	NA
SARS-CoV-2 vaccination	638	(76.5%)	3564	(65.2%)	<.001
Fully vaccinated[a]	590	(70.7%)	2685	(49.1%)	<.001
Severe SARS-CoV-2 infection	628	(75.3%)	3920	(71.7%)	.030
Concomitant treatments initiated at baseline					
Antimicrobials	458	(54.9%)	1310	(24.0%)	<.001
Antivirals	419	(50.2%)	987	(18.0%)	<.001
Molnupiravir	36	(4.3%)	518	(9.5%)	<.001
Remdesivir	39	(4.7%)	493	(9.0%)	<.001
Antibiotics	113	(13.5%)	518	(9.5%)	<.001

(Continues)

TABLE 1 (Continued)

Baseline characteristics	Nirmatrelvir/ritonavir users (N = 834)		Non-nirmatrelvir/ritonavir users (N = 5469)		p-value[d]
	N/mean	%/SD	N/mean	%/SD	
Immunomodulators	63	(7.6%)	779	(14.2%)	<.001
Dexamethasone	52	(6.2%)	699	(12.8%)	<.001
Other systemic steroid	12	(1.4%)	87	(1.6%)	.742
Interferon-β-1b	3	(.4%)	22	(.4%)	.856
Baricitinib	5	(.6%)	23	(.4%)	.471
Tocilizumab	0	(.0%)	16	(.3%)	NA
Paracetamol	92	(11.0%)	263	(4.8%)	<.001
Laboratory parameters[b]					
Cycle threshold value, cycle	21.9	7.2	22.6	8.7	.054
<20	247	(40.4%)	1343	(39.7%)	<.001
20–<30	280	(45.8%)	1359	(40.2%)	
30–<35	65	(10.6%)	362	(10.7%)	
≥35	20	(3.3%)	317	(9.4%)	
Lactate dehydrogenase, U/L	395.9	677.8	466.7	856.4	.138
C-reactive protein, mg/L	56.5	72.9	87.3	90.3	<.001
Lymphocyte, 10^9/L	1.0	.8	1.0	2.8	.663
AST, U/L	83	216	94	309	.369
ALT, U/L	279	1006	317	993	.574
Total bilirubin, μmol/L	21.4	40.6	22.8	44.6	.457
INR	1.4	.7	1.7	1.3	<.001

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine transaminase; ARB, angiotensin receptor blockers; AST, aspartate transaminase; ICU, intensive care unit; INR, international normalized ratio; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation; ULN, upper limit of normal.

[a]Fully vaccinated patients were defined as those with at least 2 doses of Comirnaty or 3 doses of CoronaVac.

[b]Age, Charlson's index, and laboratory parameters on admission are presented in mean ± SD.

[c]The calculation of Charlson's index does not include Acquired Immune Deficiency Syndrome (AIDS).

[d]*p*-values for the comparison between the nirmatrelvir/ritonavir users and non-nirmatrelvir/ritonavir users by linear regression for continuous variables, logit regression for dichotomous variables, and Chi-square test for categorical variables more than two levels.

liver disease was present in about 11% in nirmatrelvir/ritonavir users and 10% in non-users. In addition, the baseline INR (1.4 vs. 1.7, $p < .001$) were more deranged among non-users than nirmatrelvir/ritonavir users (Table 1).

3.2 | SCCS analysis

Table 2 shows the incidences of nirmatrelvir/ritonavir users who had ALI in different observation periods, and the IRRs of ALI in each risk period compared to non-exposure period and pre-exposure period, respectively. Mean durations of observation period were 85 days for nirmatrelvir/ritonavir users with ALI. Compared with the non-exposure period, ALI risk increased significantly during the pre-exposure period (IRR = 38.13, 95% CI = 29.29–49.62), remained elevated during the five-day nirmatrelvir/ritonavir treatment (IRR = 20.75, 95% CI = 17.06–25.25), and >5 days after nirmatrelvir/ritonavir initiation (IRR = 16.27, 95% CI = 13.23–20.01). Compared to the pre-exposure period, risk of ALI was not increased during the five-day nirmatrelvir/ritonavir treatment period (IRR = .54, 95% CI = .43–.70).

Similar results were found in the subgroup (Figure 3, Table S2) and sensitivity (Table S3) analyses. Results of the subgroup and sensitivity analyses were generally comparable to those of the main analysis, where increased risk of ALI was consistently observed during the pre-exposure period and nirmatrelvir/ritonavir treatment compared to non-exposure period, and not significantly higher during nirmatrelvir/ritonavir treatment when compared with the pre-exposure period. While censoring effect was present (Figure S3), the results by event-dependent observation period were consistent with the main results.

3.3 | Clinical presentation and severity of ALI among subjects with ALI during risk periods

Among 2 255 995 adult COVID-19 patients without use of nirmatrelvir/ritonavir and without ALI before the diagnosis of SARS-CoV-2

TABLE 2 Comparison of risks of acute liver injury between different risk periods.

Nirmatrelvir/ritonavir (N = 834)	N	Events	Rate	Person-days	Non-exposure period as reference			Pre-exposure period as reference			Exposure period as reference		
					IRR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value
Pre-exposure period	441	131	29.7%	1821	38.13	(29.29, 49.62)	<.001	(reference)			1.84	(1.44, 2.35)	<.001
Exposure period	834	298	35.7%	4107	20.75	(17.06, 25.25)	<.001	.54	(.43, .70)	<.001	(reference)		
Wash-out period	799	204	25.5%	3875	16.27	(13.23, 20.01)	<.001	.43	(.33, .55)	<.001	.78	(.65, .94)	.009
Non-exposure period	744	201	27.0%	80 663	(reference)			.03	(.02, .03)	<.001	.05	(.04, .06)	<.001

Note: Observation period: From COVID-19 diagnosis or symptom onset date (whichever the earliest) to 12th February 2023. Patients were censored on the date of death. Pre-exposure period: From COVID-19 diagnosis or symptom onset date (whichever the earliest) to the day before nirmatrelvir/ritonavir initiation. Exposure period: 0–4 days after nirmatrelvir/ritonavir initiation. Wash-out period: 5–9 days after nirmatrelvir/ritonavir initiation. Non-exposure period: ≥10 days after nirmatrelvir/ritonavir initiation.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

infection, 5469 (.2%) non-nirmatrelvir/ritonavir users had incident ALI during the observation period. The median time from the diagnosis of SARS-CoV-2 infection to ALI onset was 4 days (IQR: 1–12). And 23.7% of the ALI cases were mild in severity, while moderate, moderate-to-severe, and severe or fatal cases were seen in 35.4%, 31.7%, and 9.2%, respectively. And 743 (13.6%) patients required ICU admission, and 70 (1.3%) patients had liver decompensation (Table 3).

Among 153 853 adult COVID-19 patients with use of nirmatrelvir/ritonavir and without ALI before the diagnosis of SARS-CoV-2 infection, 834 (.5%) nirmatrelvir/ritonavir users had incident ALI during the observation period. The median time from the diagnosis of SARS-CoV-2 infection to ALI onset was 6 days (IQR: 1–11). And 44.8% were mild in severity, and moderate, moderate-to-severe, and severe or fatal cases were seen in 30.5%, 18.9% and 5.8%, respectively. And 106 (12.7%) patients required ICU admission after incident ALI, and 8 (1.0%) patients had liver decompensation (Table 3).

Compared to non-nirmatrelvir/ritonavir users, nirmatrelvir/ritonavir users had less severe ALI by the DILI severity index ($p < .001$), with lower peak INR (1.7 vs. 2.3; diff = −.5; $p < .001$). Nirmatrelvir/ritonavir users and non-users had comparable rates of ICU admission (12.7% vs. 13.6%; odds ratio [OR] = .90; $p = .408$) and liver decompensation (1.0% vs. 1.3%; OR = .62; $p = .230$). Among nirmatrelvir/ritonavir users with ALI, there were 243 (29.1%) all-cause deaths during the observation period, including 153 deaths occurred during the non-exposure period. There were 2138 (39.1%) death cases among non-nirmatrelvir/ritonavir users with ALI. ALI cases with nirmatrelvir/ritonavir use had lower risk of all-cause death than non-users (29.1% vs. 39.1%; OR = .64; $p < .001$) (Table 3).

4 | DISCUSSION

Nirmatrelvir/ritonavir is authorized for oral use in mild-to-moderate COVID-19 patients to reduce the risk of progression to severe disease. It should be initiated within 5 days of symptom onset, provided that there are no contraindications. Earlier studies have showed that a full dose of 400 mg ritonavir was associated with a higher risk of liver injury, while a lower dose of ritonavir of less than 200 mg was not significantly associated with an increased risk of liver injury, even in HIV and viral hepatitis co-infected patients.[27] In the treatment regimen of nirmatrelvir/ritonavir, the daily dosage of the protease inhibitor is 200 mg, thereby reducing the risk of developing liver injury from ritonavir. The current dosage of nirmatrelvir/ritonavir has demonstrated a good safety profile as evidenced by the mild or insignificant increases in ALT levels with no cases of clinically apparent liver injury reported in clinical trials.[28,29]

Meanwhile, in the real-world setting, the pharmacokinetics of nirmatrelvir/ritonavir is less predictable. Since ritonavir-boosted nirmatrelvir is metabolized by CYP3A, potential hepatotoxicity may arise from drug accumulation and drug–drug interactions.[28,30] Therefore, sole treatment of nirmatrelvir/ritonavir or reducing the dose of other treatments is generally recommended to avoid potential drug

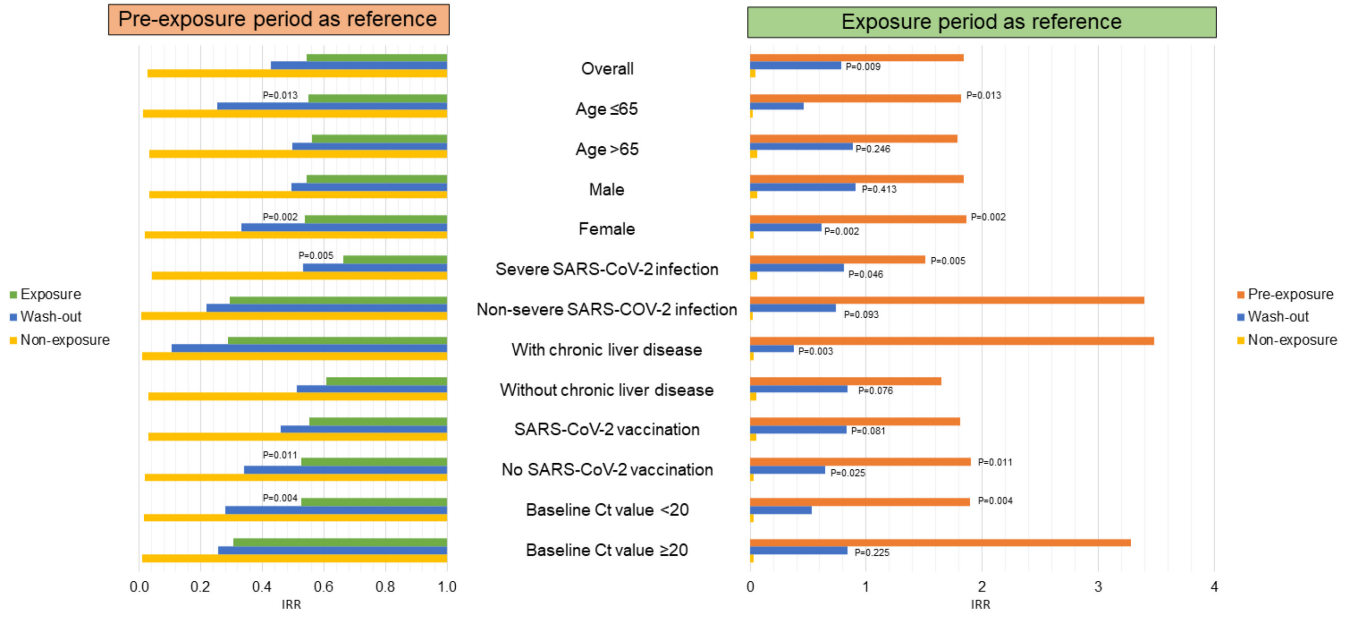


FIGURE 3 Comparison of risks of acute liver injury between different risk periods taking pre-exposure period as reference (left panel) and exposure period as reference (right panel) in overall and by subgroups of age groups, gender, infection severity, chronic liver disease status, SARS-CoV-2 vaccination status, and baseline Ct value. All p < .001 unless otherwise specified.

TABLE 3 Severity of acute liver injury in nirmatrelvir/ritonavir users and non-nirmatrelvir/ritonavir users.

	Nirmatrelvir/ritonavir (*N* = 834)		Non-nirmatrelvir/ritonavir (*N* = 5469)		Difference/Odds ratio[a]	
Severity of acute liver injury	***N*/Mean**	**%/SD**	***N*/Mean**	**%/SD**		***p*-value**
Drug-induced liver injury (DILI) severity index						
Mild	374	(44.8%)	1294	(23.7%)		<.001
Moderate	254	(30.5%)	1935	(35.4%)		
Moderate to severe	158	(18.9%)	1736	(31.7%)		
Severe or fatal	48	(5.8%)	504	(9.2%)		
Peak AST, U/L	401	1100	450	1137	−66	.316
Peak ALT, U/L	276	450	269	594	27	.234
Peak total bilirubin, μmol/L	32.1	54.1	33.9	58.4	−2.0	.372
Peak INR	1.7	1.0	2.3	1.8	−.5	<.001
Events after acute liver injury						
ICU admission	106	(12.7%)	743	(13.6%)	.90	.408
Liver decompensation	8	(1.0%)	70	(1.3%)	.62	.230
Ascites	6	(.7%)	46	(.8%)	.83	.691
Liver encephalopathy	1	(.1%)	22	(.4%)	NA	NA
Jaundice	0	(.0%)	8	(.1%)	NA	NA
Liver transplantation	1	(.1%)	1	(.0%)	NA	NA
Death	243	(29.1%)	2138	(39.1%)	.64	<.001

Note: Odds ratios were estimated only if number of events were at least 2 in both groups.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate transaminase; eGFR, Estimated glomerular filtration rate; ICU, Intensive Care Unit; INR, International normalized ratio;

[a]Odds ratios were estimated by logistic regression for ICU admission, liver decompensation, and death, and ordered logistic regression for DILI severity index. Differences were estimated by linear regression for peak AST, peak ALT, and peak AST-to-ALT ratio. All regression models adjusted for age, sex, Charlson's index, chronic liver disease, SARS-CoV-2 severity, vaccination status, use of antibiotics, remdesivir, molnupiravir, and month of infection.

interactions.[3,30] Our results are consistent with the data from clinical trials and suggest that initiation of nirmatrelvir/ritonavir does not increase the risk of liver injury to COVID-19 patients in a cohort where the majority of patients was above age 65, on concomitant medications and suffer from chronic medical comorbidities, in which chronic liver disease was present in 11% of subjects. Elevations of ALT are mostly mild, and serious adverse effects are uncommon.

A number of potential mechanisms might account for the observed liver injury events in nirmatrelvir/ritonavir users. Alterations to CYP3A activity during the course of COVID-19 infection influence systemic exposure of the drug. In addition, inflammation from immune rebound following treatment with antivirals may lead to drug hepatotoxicity.[31] Some studies have concluded that drug-induced systemic inflammation, especially those for COVID-19 infection, and pneumonia-associated hypoxia result in liver injury in COVID-19 patients. In these studies, distinguishing between the hepatic dysfunctions induced by a drug or attributed to SARS-CoV-2 infection is difficult because some of the patients had been put on lopinavir/ritonavir plus interferon α-2b.[32] At the same time, the downregulation of CYPs enzymes could be caused by an elevation of cytokines and interleukins (especially interleukin-6) due to cytokine storm syndrome in COVID-19[33]; yet, the effect of cytokine storm may be marginal on ritonavir exposure, which is likely explained by the fact that ritonavir inhibits its own metabolism.[34] Furthermore, there is evidence that the SARS-CoV-2 virus itself can cause liver damage by directly binding to angiotensin-converting enzyme 2 (ACE2) receptors on cholangiocytes and hepatocytes.[35,36] Liver damage during SARS-CoV-2 infection has been reported in patients with and without previous liver diseases.[37] Such liver injury has been manifested as significant elevation of ALT and AST levels, affecting 15–62% of patients with or without a significant increase in bilirubin levels. Most of these alterations are characterized by the presence of mild-to-moderate transient increases, and are related to the severity of the viral infection. Autopsies of some patients who died from SARS-CoV-2 infection have shown signs related to hepatic steatosis and portal inflammation.[38] Our study has not identified a significantly higher risk of ALI following nirmatrelvir/ritonavir initiation. Elevation of aminotransferase levels was mainly observed during the pre-exposure period, which was likely attributed to the underlying SARS-CoV-2 infection or use of other medications, rather than to nirmatrelvir/ritonavir. Moreover, the highest risk period of ALI was observed in the pre-exposure period, regardless of vaccination status, viral load, severity of COVID-19 infection, and concomitant chronic liver disease, highlighting the robustness of the findings regarding the temporal relationship between drug exposure and ALI.

Our results suggest that the severity of DILI and peak INR values were lower among nirmatrelvir/ritonavir users than non-users, with no increase in risk of ICU admission and liver decompensation (Table 3). This is consistent with a previous study that revealed a minimal risk of liver injury following nirmatrelvir/ritonavir initiation.[4] Notably, patients prescribed with nirmatrelvir/ritonavir were representative of an ill population (older, more chronic liver disease, more severe infection, higher viral load) with high-risk of complications from SARS-CoV-2 infection (Table S1). Despite these baseline differences, nirmatrelvir/ritonavir users with ALI in our cohort had better laboratory and clinical outcomes compared to non-users with ALI. Therefore, it is likely that nirmatrelvir/ritonavir use has not contributed significantly to the ALI, while the SARS-CoV-2 infection itself, and the severity of infection, may have had a larger effect on liver injury. The findings from our current study in the real-world setting are in line with the lower incidence of hepatic dysfunction among nirmatrelvir/ritonavir users compared to the placebo group in the pivotal EPIC-HR trial.[3]

While our results show that nirmatrelvir/ritonavir use is unlikely associated with a significantly increased risk of ALI in the context of SARS-CoV-2 infection, several limitations should be noted in the current study. Firstly, results of liver biopsy and liver ultrasound were not available in our data source; and only laboratory data of ALT, AST, total bilirubin, and INR were used for outcome definition. The dataset also did not contain sufficient information to evaluate the factors related to severe or fatal ALI, and the sequence of events leading to adverse clinical outcomes following ALI (ICU admission, liver transplantation and liver decompensation). Secondly, diagnosis of pre-existing cases unmasked, and under-diagnosis of asymptomatic cases could not be completely ruled out. Lastly, with the assumption used in SCCS analysis, only new-onset ALI, but not recurrent events, were included in the current analysis. Therefore, future studies are needed to explore the risk of ALI following nirmatrelvir/ritonavir use in patients with previous episode(s) of ALI.

5 | CONCLUSIONS

In conclusion, ALI was mainly observed during the pre-exposure period in nirmatrelvir/ritonavir users, and are mostly mild in severity. Based on current findings and all available evidence, nirmatrelvir/ritonavir can be safely prescribed according to clinical indications without an apparent increase in ALI risk, among COVID-19 patients with and without pre-existing chronic liver diseases. Although the risk of severe or fatal ALI is unlikely related to nirmatrelvir/ritonavir use, ALI during the course of SARS-CoV-2 infection is not uncommon, necessitating close monitoring of liver function regardless of nirmatrelvir/ritonavir use.

AUTHOR CONTRIBUTIONS

CKHW and LYM were responsible for the study concept. CKHW, LYM, ICHA reviewed the literature, designed statistical analysis, conducted analyses, wrote the manuscript; ICHA conducted analyses; WYC and CHS wrote the manuscript; CKHW, LYM, ICHA, WYC, CHS, KTKL, EHYL, BJC, GML, and MFY contributed to the interpretation of the analysis, critically reviewed and revised the manuscript. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The clinical outcome data were extracted from the Hospital Authority database in Hong Kong and vaccination records were extracted from the eSARS data provided by the Centre for Health Protection. The data custodians (the Hospital Authority and the Department of Health of Hong Kong SAR government) 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 for this study. Authors must not transmit or release the Data, in whole or in part and in whatever form or media, or any other parties or place outside Hong Kong; and fully comply with the duties under the law relating to the protection of personal data including those under the Personal Data (Privacy) Ordinance and its principles in all aspects.

ETHICS APPROVAL AND INFORMED CONSENT

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW 20–493). Individual patient informed consent was not required for this retrospective cohort study using anonymised data.

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SUPPORTING INFORMATION

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

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