ORIGINAL ARTICLE

Assessment of Potential Drug-Drug Interactions between Nirmatrelvir/Ritonavir and Concomitant Drugs among Coronavirus Disease Patients in a Tertiary Care Hospital.

Shamala Balan*, Kavidha Mohan.

Pharmacy Department, Hospital Tengku Ampuan Rahimah, Jalan Langat, 41200 Klang, Selangor, Malaysia.

Corresponding Author
Shamala Balan
Pharmacy Department, Hospital Tengku Ampuan Rahimah, Jalan Langat, 41200 Klang, Selangor, Malaysia.
Email: shamala.balan@moh.gov.my; shamala.balan@gmail.com

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Abstract
Background: Nirmatrelvir/ritonavir is indicated for the treatment of COVID-19infection. However, potential drug-drug interactions (pDDI) between nirmatrelvir/ritonavir and concomitant drugs require further investigation.
Objective: To assess the prevalence, management, and risk factors of pDDI between nirmatrelvir/ritonavir and concomitant drugs in patients with COVID-19 .
Methods: This cross-sectional study was approved by the Medical Research Ethics Committee of Malaysia. Inclusion criteria were COVID-19 patients aged ≥18 years, treated with nirmatrelvir/ritonavir between July and September 2022 in a tertiary care hospital in Selangor. Classification and management of pDDI were categorised according to the University of Liverpool COVID-19 Drug Interactions classification. The pDDI management in clinical practice was compared to the recommended classifications and categorised as 'compliant' or 'non-compliant. Patient characteristics were analysed descriptively. Binary logistic regression was used to identify pDDI risk factors.
Results: The study included 189 patients with a mean age ±SD of 56.76±18.68 years. Comorbidities and polypharmacy were observed in 147 (77.78%) and 73 (38.62%) patients, respectively. A total of 114 patients (60.32%) were reported to have at least one pDDI with nirmatrelvir/ritonavir. Most concomitant drugs had potential interactions with nirmatrelvir/ritonavir (n=152, 77.16%). Compliance with the recommended pDDI management was observed in 174 (88.32%) drug entries. Age (OR 1.04; 1.02-1.06; p=0.001), comorbidities (OR 8.87; 3.17-24.78; p<0.001), and polypharmacy (OR 6.76; 2.74-16.65; p<0.001) were significant risk factors of pDDI with nirmatrelvir/ritonavir.
Conclusion: Prevalence of pDDI among COVID-19 patients treated with nirmatrelvir/ritonavir was high and mainly compliant with the recommended pDDI management. Age, comorbidities, and polypharmacy were pDDI risk factors, warranting a case-by-case multidisciplinary approach to optimise treatment with nirmatrelvir/ritonavir.

Keywords: *Comorbidities, COVID-19, Drug interactions, nirmatrelvir and ritonavir drug combination, polypharmacy.*

Introduction

Within a month of its emergence, the coronavirus disease 2019 (COVID-19) was declared an international public health emergency by the World Health Organization (WHO). Alongside advancements in detection methods and prevention strategies, significant attention was given to developing treatment plans for COVID-19. This led to the United States Food and Drug Administration (USFDA) issuing an Emergency Use Authorization (EUA) for the unapproved product nirmatrelvir/ritonavir in December 2021. This combination is intended for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years and older, weighing at least 40 kg) who have tested positive for SARS-CoV-2 and are at high risk of progressing to severe COVID-19, including hospitalization or death [1]. In this context, high-risk adults included those meeting any of the following criteria: aged ≥ 60 years, immunocompromised, having comorbidities, obese, current or former smokers, and unvaccinated or having received incomplete vaccination [2]. The treatment of COVID-19 with nirmatrelvir 300 mg/ritonavir 100 mg twice daily for 5 days in high-risk adult patients who experienced mild to moderate symptoms within 5 days of illness [2] began in Malaysia in April 2022 [3]. For patients with renal impairment (eGFR 30-60 mL/min), a renal-adjusted dose of nirmatrelvir 150 mg/ritonavir 100 mg twice daily for 5 days is recommended [2]. Nirmatrelvir is an inhibitor of the SARS-CoV-2 3CL-like protease, which prevents the cleavage of polyproteins necessary for viral genome replication. It is administered in combination with ritonavir, a medication that inhibits hepatic enzymes, thereby slowing the metabolism of nirmatrelvir and increasing its concentration [4]. However, the addition of ritonavir introduces the risk of potential drug-drug interactions (pDDI) due to its effects on cytochrome P450 3A4. Pharmacists were involved in procurement, supply, monitoring, pDDI management, and reporting adverse drug reactions of nirmatrelvir/ritonavir [3].

A few studies have evaluated the extent and nature of pDDI between nirmatrelvir/ritonavir and other drugs commonly prescribed to adult patients [5–7]. The prevalence of pDDI involving nirmatrelvir/ritonavir ranged between 16.2% and 68% , reported to be higher among the elderly patients and in the community settings [5-9]. An analysis of a large database in the US on pDDI between nirmatrelvir/ritonavir and commonly prescribed drugs to patients at high risk of developing COVID-19 complications showed that most drugs are unlikely to have pDDI with nirmatrelvir/ritonavir [10]. Age , gender , smokers , polypharmacy , history of solid organ transplant , and presence of co-morbidities were identified as the risk factors of developing pDDI between nirmatrelvir/ritonavir and other drugs [5,6].

Most existing evidence on pDDI with nirmatrelvir/ritonavir were derived from case reports and case series involving a certain drug , drug class , and specific group of patients [11-14]. The vast scarcity of evidence derived from real-world data on the prevalence, management, and risk factors of pDDI between concomitant drugs in COVID-19 patients treated with nirmatrelvir/ritonavir, both internationally and locally, led to the conception of this study. The study aimed to determine the prevalence, management and risk factors of pDDI between nirmatrelvir/ritonavir and concomitant drugs in COVID-19 patients. Understanding the prevalence and risk factors of pDDI in patients treated with nirmatrelvir/ritonavir could inform healthcare providers on better pDDI management strategies and optimise therapeutic outcomes for COVID-19 patients.

Materials and methods

Reporting considerations

The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15]. During the preparation of this work, the authors used ChatGPT to improve readability and

language. After using the tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the article.

Study design and site

The retrospective study conducted at a 1261-bed tertiary care hospital in the central region of Peninsular Malaysia. During the COVID-19 pandemic, the study site provided inpatient and outpatient treatment to COVID-19 patients. Warning signs for considering inpatient treatment included: fever of more than 2 days, SPpO2 < 95% (at rest or after exertion), angina or chest pain, dehydration or not passing urine for more than 8 hours, inability to ambulate without assistance, or reduced level of consciousness [16]. The treatment for COVID-19 using nirmatrelvir/ritonavir started in June 2022 at the study site. The pharmacy department adhered to a consensus workflow for screening and supplying nirmatrelvir/ritonavir as well as providing patient counselling. Data from manual prescriptions for nirmatrelvir/ritonavir and concomitant drugs were entered into the Pharmacy Information System (PhIS) version 2.6.3.13. An assessment form was used to record patient's demographic and clinical characteristics, assess patient's eligibility criteria using a risk-stratified scoring system [17], record patient's current medications, and track medication counselling provision during the 5-day treatment with nirmatrelvir/ritonavir.

Sample size calculation

The sample size was calculated using the formula proposed in a previous study [18]. For the period of June to December 2022, a total of 1,479,401 cumulative COVID-19 cases were reported in the state of Selangor [19]. Among these cases, about 76% involved individuals aged 18 years and above (19), yielding the total cases among those eligible for nirmatrelvir/ritonavir treatment (age-wise) to be 1,124,345. From June to December 2022, a total of 9716 patients were prescribed with nirmatrelvir/ritonavir for the treatment of COVID-19 (unpublished data, Pharmacy Services Division, Selangor State Health Department, obtained with permission on 9 January 2023). Accordingly, the estimated prevalence of nirmatrelvir/ritonavir treatment for eligible patients was 0.86%.

Using 0.86 prevalence rate for patients prescribed with nirmatrelvir/ritonavir, precision value of 0.05, and a Z-value of 1.96, the formula yielded a minimum sample size of 185 patients.

Eligibility criteria

Adult patients diagnosed with COVID-19 and prescribed with nirmatrelvir/ritonavir as inpatients or outpatients at the study site between July and September 2022 were included in the study. Patients with incomplete or missing drug data were excluded. Additionally, patients who refused nirmatrelvir/ritonavir treatment after prescription issuance were also excluded from the study.

Data source

The nirmatrelvir/ritonavir treatment assessment forms as along with inpatient, outpatient, and discharge prescriptions, were used as source documents to obtain patient and drug data. The PhIS was used to retrieve additional information on medication counselling notes and to cross-verify the drug data.

Data collection

The data was collected using a structured, validated, and piloted data collection form, which included patient characteristics (age, weight, gender, ethnicity), renal function status, presence and types of comorbidities, and presence of COVID-19 X-ray changes. The COVID-19 X-ray changes were documented as present or not present. Prescribers considered features of severe pneumonia, multi-lobular involvement, or rapidly worsening chest X-ray [2] as COVID-19 X-ray changes.

The number and types of concomitant drugs were also recorded. Concomitant drugs included those that the patients were taking at the onset of and

during nirmatrelvir/ritonavir treatment. The presence of polypharmacy was determined if five or more concomitant drugs were prescribed to the patients [20]. Patients with at least one concomitant drug that has a pDDI with nirmatrelvir/ritonavir were classified as the pDDI group. In keeping with a previous study, patients with concomitant drugs that do not have a pDDI with nirmatrelvir/ritonavir or no concomitant drugs were classified as the non-pDDI group [6].

Potential drug-drug interaction was classified as; do not co-administer, potential interaction, potential weak interaction, or no interaction using established drug-drug interaction resources and references, in the following order, the University of Liverpool COVID-19 Drug Interactions checker [21], the Micromedex Drug Interactions checker, package insert, or literature review. For fixed-dose combination (FDC) drugs, pDDI were assessed for each drug in the FDC with nirmatrelvir/ritonavir, and the highest level of pDDI was assigned. The pDDI management as recommended by the University of Liverpool COVID-19 Drug Interactions checker was recorded which included withholding, dose reduction, or no dosage adjustment [21]. It is noteworthy that one drug may have more than one recommendation for pDDI management. For example, the pDDI between amlodipine and nirmatrelvir/ritonavir may be managed by a 50% dose reduction or withholding the drug, with advice to the patient to monitor for symptoms of hypotension [21]. The pDDI management in clinical practice was compared with the recommended pDDI management and classified as 'compliant' or 'non-compliant' [21-22].

The data were collected independently by two researchers who cross-checked each other's work. Any discrepancies were resolved through discussion between the researchers. In the event of disagreement, a senior pharmacist was consulted for clarification, and consensus was reached to finalize the decision.

Data analysis

Data were analysed using Microsoft Excel 2011 and SPSS 20.0 software. Mean and standard deviation (SD) were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Univariable analysis was performed to screen for significant independent variables. The independent variables with a p-value < 0.25 and clinical significance were considered into the multivariable binary logistic regression.

Binary logistic regression was performed for the multivariable analysis. Forward, backward, forward stepwise and backward stepwise methods were applied. Multicollinearity and interaction test were conducted to ensure no correlation and interaction between independent variable in the final model. The preliminary main effect model was chosen based on the principle of the best model with the best fit, clinically plausible and statistically significant, using the Hosmer-Lemeshow test, classification table, and the area under the Receiver Operating Characteristic (ROC) curve. The adjusted odds ratio, regression coefficient, 95% confidence interval, Wald statistic was presented and p-values < 0.05 were considered statistically significant.

Results

During the study period, 191 patients were prescribed with nirmatrelvir/ritonavir. However, two patients were excluded due to missing drug data. Consequently, 189 COVID-19 patients prescribed and treated with nirmatrelvir/ritonavir during the study period were included in the study. The mean age (SD) was 56.76 (18.68) years (Table 1). The most reported comorbidities were hypertension (n=102, 53.97%), diabetes mellitus (n=73, 38.62%), and cardiovascular diseases (n=39, 20.63%).

Concomitant drug entries were recorded for 159 (84.13%) patients, involving 753 drug entries, which mostly involved atorvastatin (n=60, 7.97%), pantoprazole (n=56, 7.44%), and amlodipine (n=46, 6.11%). In total, 114 (60.32%)

patients were on 197 (26.16%) drug entries leading to pDDI with nirmatrelvir/ritonavir. The pDDI classified as do not co-administer, potential interaction, and potential weak interaction involved 10.15% (n=20), 77.16% (n=152), and 12.69% (n=25) drug entries, respectively. The pDDI was managed by withhold, dose reduction, and no dose adjustment in 55.84% (n=110), 18.27% (n=36), and 25.89% (n=51) drug entries, respectively (Table 2). The most common concomitant drugs involved in pDDI were atorvastatin (n=60, 30.46%), amlodipine (n=47, 23.85%), clopidogrel (n=18, 9.14%), simvastatin (n=14, 7.11%), and diphenhydramine (n=7, 3.55%). The comparison between the pDDI management in clinical practice and the recommended pDDI management is presented in Table 2. Compliance to the recommended pDDI management were observed in 174 (88.32%) drug entries.

Univariable analysis identified age, weight, elderly, obesity status, patient type (i.e. inpatient vs outpatient), presence of co-morbidities, number of co-morbidities, nirmatrelvir/ritonavir dosing, presence of COVID-19 x-ray changes, number of concomitant drugs, and polypharmacy as significant factors. Binary logistic regression analysis identified age (OR 1.04; 1.02-1.06; p=0.001), comorbidity (OR 8.87; 3.17-24.78; p<0.001), and polypharmacy (OR 6.76; 2.74-16.65; p<0.001) as pDDI risk factors (Table 3).

Discussion

The current study identified the prevalence, management and risk factors of pDDI involving nirmatrelvir/ritonavir and concomitant drugs prescribed to COVID-19 patients in tertiary care hospital using real-world data. The prevalence of pDDI between nirmatrelvir/ritonavir and concomitant drugs among COVID-19 patients identified in this study (60.32%) was lower than the rate reported in a local primary care setting [22], but comparable to a study conducted among hospitalised patients [7]. This could be explained by the high proportion of COVID-19 patients who received treatment as inpatient, whereby incidence of pDDI were reported to be higher in inpatients as compared to outpatients [23]. This is because hospital stays increase the likelihood of taking multiple drugs, which subsequently raises the risk of potential DDIs [24].

About 77% of the drug entries involved in pDDI were found to have potential interaction with nirmatrelvir/ritonavir. Almost 90% of pDDIs were managed in compliance with the recommended guidelines for pDDI management, leaving approximately 10% as non-compliant. A local study reported a higher non-compliance rate of 21.7% for recommended pDDI management [22]. This disparity may be attributed to differences in study settings but is primarily due to variations in the parameters used to calculate the proportion of non-compliance. In our study, the proportion was determined based on the number of non-compliant drug entries relative to the total number of drug entries. In contrast, the previous study [22], calculated non-compliance based on the types of non-compliant drugs relative to the total types of drugs. Nevertheless, the observed non-compliance can be explained by the application of clinical judgment in real-life pDDI management. This involves risk-benefit assessment by taking treatment goal, patient, and concomitant drug factors into consideration before withholding or reducing the dose of any drugs with pDDI, especially among those with multimorbidity and polypharmacy [25].

About 26% of the concomitant drugs prescribed to the COVID-19 patients posed a risk of pDDI with nirmatrelvir/ritonavir. This finding concurred with the rate reported in the US, whereby 30% of the top 100 drug-prescribed drug were expected to cause pDDI with nirmatrelvir/ritonavir [10]. Concomitant drugs with pDDI involving nirmatrelvir/ritonavir were mainly drugs for cardiovascular diseases. This finding highlighted the need for a specific decision-making algorithm for patients on cardiovascular drugs who needs nirmatrelvir/ritonavir as treatment for COVID-19 [25]. Statins are often involved in pDDI with

nirmatrelvir/ritonavir, but a previous study [6] found similar pDDI prevalence even without statins.

Age, comorbidity, and polypharmacy were identified as pDDI risk factors. Similar findings were reported in previous studies [5,6]. Elderly or people with comorbidity benefit the most from treatment with nirmatrelvir/ritonavir [26]. However, polypharmacy is frequently observed in the same population. Instead of depriving eligible patients from treatment with nirmatrelvir/ritonavir, anticipatory deprescribing practice, as proposed by Ross et al. may be considered to enhance the access and use of nirmatrelvir/ritonavir in eligible patients [8].

The strength of the study relies on the use of real-world data to assess pDDI in inpatient and outpatient setting, which is a typical scenario in most healthcare facilities in Malaysia and other countries. However, the study is limited by data to further assess the outcome of pDDI in patients treated with nirmatrelvir/ritonavir. Additionally, information on smoking status was not adequately captured in study source documents, making it impossible to assess if smoking status was a risk of pDDI in patients treated with nirmatrelvir/ritonavir. Future prospective studies could overcome incomplete or missing data issues. Moreover, future studies could explore the implementation and impact of personalised approaches such as disease-specific decision-making algorithms and anticipatory deprescribing practice in managing pDDI in nirmatrelvir/ritonavir patients.

Conclusion

The study revealed a high prevalence of potential drug-drug interactions among patients treated with nirmatrelvir/ritonavir, which were mainly compliant to the recommended pDDI management. Age, comorbidity, and polypharmacy were pDDI risk factors. A case-by-case approach is warranted in optimising treatment of COVID-19 patients with nirmatrelvir/ritonavir.

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Authors contribution

Both authors SB and KM contributed to conceptualisation, data management, synthesis and analysis, writing, reviewing, and finalizing the manuscript.

Declaration of conflicting interests

The authors declares that there is no conflict of interest.

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Table 1. Demographic and clinical characteristics of patients included in the study

Characteristics	With pDDI (n=114), n (%)	Without pDDI (n=75), n (%)	Total (n=189), n (%)	p-value
Age (years), mean ± SD	63.04 ± 14.79	47.2 ± 19.98	56.76 ± 18.68	<0.001
Weight (kg), mean ± SD	68.75 ± 15.94	73.14 ± 19.97	70.49 ± 17.73	0.095
Gender				
Male	68 (59.65)	39 (52)	107 (56.61)	0.299
Female	46 (40.35)	36 (48)	82 (43.39)	
Ethnicity				
Malay	57 (50)	32 (42.67)	89 (47.09)	
Chinese	25 (21.93)	21 (28)	46 (24.34)	0.71
Indian	30 (26.32)	20 (26.67)	50 (26.46)	
Others	2 (1.75)	2 (2.67)	4 (2.12)	
Elderly (≥60 years)				
Yes	75 (65.79)	25 (33.33)	100 (52.91)	<0.001
No	39 (34.21)	50 (66.67)	89 (47.09)	
Obese				
Yes	16 (14.04)	21 (28)	37 (19.58)	0.019
No	98 (85.96)	54 (72)	152 (80.42)	
Patient type				
Inpatient	91 (79.82)	49 (65.33)	140 (74.07)	0.026
Outpatient	23 (20.18)	26 (34.67)	49 (25.93)	
Immunocompromised				
Yes	14 (12.28)	8 (10.67)	22 (11.64)	0.735
No	100 (87.72)	67 (89.33)	167 (88.36)	
Presence of comorbidities				
Yes	108 (94.74)	39 (52)	147 (77.78)	<0.001
No	6 (5.26)	36 (48)	42 (22.22)	
Number of comorbidities				
0	6 (5.26)	36 (48)	42 (22.22)	
1	36 (31.58)	28 (37.33)	64 (33.86)	
2	39 (34.21)	8 (10.67)	47 (24.87)	<0.001
3	25 (21.93)	3 (4)	28 (14.81)	
4	7 (6.14)	0 (0)	7 (3.7)	
5	1 (0.88)	0 (0)	1 (0.53)	

Characteristics	With pDDI (n=114), n (%)	Without pDDI (n=75), n (%)	Total (n=189), n (%)	p-value
Paxlovid dosing				
Full-dose	69 (60.53)	63 (84)	132 (69.84)	0.001
Renal-adjusted dose	45 (39.47)	12 (16)	57 (30.16)	
Covid-19 X-ray changes				
Yes	39 (34.21)	19 (25.33)	58 (30.69)	0.195
No	75 (65.79)	56 (74.67)	131 (69.31)	
Polypharmacy				
Yes	65 (57.02)	8 (10.67)	73 (38.62)	<0.001
No	49 (42.98)	67 (89.33)	116 (61.38)	
Number of concomitant drugs, mean ± SD	5.25 ± 2.98	2.89 ± 2.12	3.85 ± 3.19	<0.001

pDDI: potential drug-drug interactions; SD: standard deviation

Table 2. Category of interaction and compliance to recommended intervention for drugs involved in potential drug-drug interaction with nirmatrelvir/ritonavir (drug entries, n = 197).

Drugs (number of drug entries)	**University of Liverpool COVID-19 pDDI classification** (21)	**University of Liverpool COVID-19 drug interactions recommendation** (21)	**Number of drug entries withheld (%)**	**Number of drug entries with dose adjusted (%)**	**Number of drug entries with no dose adjustment (%)**	**Number of compliance to recommended intervention (%)**
Atorvastatin (n=60)	Potential interaction	Avoid co-administration or use the lowest possible dose.	59(98.33)	1 (1.67)	0	60 (100)
Amlodipine (n=45)	Potential interaction	Reduce dose by 50% or take it every other day or withhold and advice patients to monitor for symptoms of hypotension.	14(31.11)	31(68.89)	0	45 (100)
Clopidogrel (n=18)	Potential interaction	Avoid co-administration.	5 (27.78)	0	13 (72.22)	5 (27.78)
Simvastatin (n=14)	Do not co-administer	Contraindicated – Withhold.	14 (100)	0	0	14 (100)
Diphenhydramine (n=7)	Potential weak interaction	No dosage adjustment is needed.	0	0	7 (100)	7 (100)
Felodipine (n=6)	Potential interaction	A dose reduction of 50% or taking the dose every other day could be considered, if necessary, to temporarily pause the antihypertensive drug if needed.	4 (66.67)	1 (16.67)	1 (16.67)	5 (83.33)
Dexamethasone (n=6)	Potential interaction	A dose reduction of 50% and the usual dose resumed 3 days after completing nirmatrelvir/ritonavir treatment.	2 (33.33)	0	4 (66.67)	0
Loratadine (n=5)	Potential weak interaction	No dosage adjustment is needed.	0	0	5 (100)	5 (100)
Losartan (n=4)	Potential weak interaction	No dosage adjustment is needed.	0	0	4 (100)	4 (100)
Diazepam (n=2)	Do not co-administer	Contraindicated – Withhold.	2 (100)	0	0	2 (100)
Midazolam (parenteral) (n=2)	Potential interaction	Administered with caution and close monitoring. Dosage reduction for midazolam should be considered if more than a single dose of midazolam is administered.	0	0	2 (100)	2 (100)
Rosuvastatin (n=2)	Potential interaction	Avoid co-administration or use the lowest possible dose.	2 (100)	0	0	2 (100)

Drugs (number of drug entries)	**University of Liverpool COVID-19 pDDI classification** (21)	**University of Liverpool COVID-19 drug interactions recommendation** (21)	**Number of drug entries withheld (%)**	**Number of drug entries with dose adjusted (%)**	**Number of drug entries with no dose adjustment (%)**	**Number of compliance to recommended intervention (%)**
Sodium Valproate (n=2)	Potential weak interaction	No dosage adjustment is needed.	0	0	2 (100)	2 (100)
Terazosin (n=2)	Potential interaction	No dosage adjustment is needed. Pause terazosin if hypotension occurs.	1 (50)	0	1 (50)	2 (100)
Theophylline (n=2)	Potential weak interaction	No dosage adjustment is needed.	0	0	2 (100)	2 (100)
Tramadol (n=2)	Potential interaction	No dosage adjustment is needed.	1 (50)	0	1 (50)	1 (50)
Alprazolam (n=1)	Potential interaction	Consider a lower dose.	1 (100)	0	0	0
Amlodipine/ Losartan (n=1)	Potential interaction	Reduce dose by 50% or take it every other day or withhold and advice patient to monitor for symptoms of hypotension[a]	1 (100)	0	0	1 (100)
Apixaban (n=1)	Potential interaction	Avoid co-administration or depending on apixaban dose, reduce dose by 50%.	1 (100)	0	0	1 (100)
Ciclosporin (n=1)	Do not co-administer	Dose reductions to 5-20% of the original dose with therapeutic drug monitoring if available. Otherwise use alternative COVID-19 treatment.	0	1 (100)	0	1 (100)
Digoxin (n=1)	Potential interaction	Risk/benefit evaluation or dosage adjustment based on the treatment indication and the patient's renal function.	0	0	1 (100)	1 (100)
Efavirenz (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Amlodipine/ valsartan (n=1)	Potential interaction	Reduce dose by 50% or take it every other day or withhold and advice patient to monitor for symptoms of hypotension[a]	0	1 (100)	0	1 (100)
Fluticasone/ salmeterol (n=1)	Do not co-administer	Contraindicated – Withhold[a].	1 (100)	0	0	1 (100)
Isosorbide mononitrate (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Ivabradine (n=1)	Do not co-administer	Contraindicated – Withhold.	1 (100)	0	0	1 (100)

Drugs (number of drug entries)	**University of Liverpool COVID-19 pDDI classification** (21)	**University of Liverpool COVID-19 drug interactions recommendation** (21)	**Number of drug entries withheld (%)**	**Number of drug entries with dose adjusted (%)**	**Number of drug entries with no dose adjustment (%)**	**Number of compliance to recommended intervention (%)**
Loperamide (n=1)	Potential interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Losartan / Hydrochlorothiazide (n=1)	Potential weak interaction	No dosage adjustment is needed[a].	0	0	1 (100)	1 (100)
Piribedil (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Quetiapine (n=1)	Do not co-administer	Withold or reduced to one sixth of the original dose. Original dose to be resumed 3 days after nirmatrelvir/ritonavir completion.	0	1 (100)	0	1 (100)
Tamoxifen (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Valsartan (n=1)	Potential interaction	No dose adjustment, if hypotension occurs stop valsartan.	0	0	1 (100)	1 (100)
Valsartan / Hydrochlorothiazide (n=1)	Potential interaction	No dose adjustment if hypotension occurs stop valsartan.	0	0	1 (100)	1 (100)
Zolpidem (n=1)	Potential interaction	No dosage adjustment is needed.	1 (100)	0	0	0

pDDI: potential drug-drug interaction; [a]Fixed dose combination (FDC): Highest level of potential drug-drug interaction was assigned

Table 3. Binary logistic regression of risk factors for potential drug-drug interactions with nirmatrelvir/ritonavir.

Factors	**Adjusted Odds Ratio**	**95% CI**	**P-value**
Age (years)	1.04	1.02 - 1.06	0.001
Co-morbidities	8.87	3.17 - 24.78	<0.001
Polypharmacy	6.76	2.74 - 16.65	<0.001

CI: confidence interval; Hosmer & Lemeshow p-value of the model was 0.588, with 78.8% of the subjects are correctly classified by the model and area under the curve (AUC) of 0.869, denoting good model fit.

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