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Original Research

Prevalence and management of drug–drug interaction of nirmatrelvir/ritonavir in patients with COVID-19: A real-life practice in Thailand

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Abstract

Background: Nirmatrelvir/ritonavir is a novel oral antiviral medication for coronavirus disease 2019 (COVID-19). Most international guidelines recommend nirmatrelvir/ritonavir for treating patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19. However, concerns have appeared regarding potential drug–drug interactions (DDIs) caused by CYP3A4 inhibition with ritonavir. **Objective:** This study aims to investigate the prevalence of potential drug interactions in outpatients with COVID-19 who received nirmatrelvir/ritonavir. Additionally, we evaluated the management of drug-drug interactions, 30-day hospitalization, 30-day mortality, and adverse drug events related to nirmatrelvir/ritonavir. **Methods:** This retrospective study, conducted at King Chulalongkorn Memorial Hospital in Thailand, included patients who received nirmatrelvir/ritonavir for COVID-19 treatment in the outpatient department from May to August 2022. Pharmacists encouraged physicians to check for potential drug-drug interactions (DDIs) with the patient's other medications before prescribing nirmatrelvir/ritonavir. Additionally, pharmacist followed up with the patients after they received nirmatrelvir/ritonavir. The DDIs were categorized as "potentially clinically significant interactions" or "should not be co-administered" based on the Liverpool Drug assessments. **Results:** Of the 221 prescriptions analyzed, 138 (62.4%) had at least one pair of DDIs, causing a total of 184 interactions determined with nirmatrelvir/ritonavir. The most prevalently involved drugs in interactions with nirmatrelvir/ritonavir were simvastatin (32.6%), atorvastatin (28.3%), and manidipine (17.4%). Of the prescriptions, 106 (57.6%) were intervened by physicians following the protocol or recommendation from the database, with statins being the most intervened group. Calcium channel blockers, such as manidipine and lercanidipine, were the most common group observed for drug interactions. The observed group involved three patients suspected of adverse drug events. A total of 13 (5.9%) patients were hospitalized but not drug interactions-related. The most predominant adverse drug reaction for nirmatrelvir/ritonavir was dysgeusia (51.1%). Conclusion: Our study emphasizes the importance of evaluating and managing potential DDIs associated with nirmatrelvir/ritonavir in COVID-19 patients. Implementing protocols to check for interactions before prescription is crucial along with developing comprehensive monitoring strategies.

Keywords: prevalence; drug interactions; nirmatrelvir/ritonavir; COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 virus, rapidly became a global health crisis since its emergence in late 2019.[1] The disease is known for its high transmission rate and diverse range of symptoms.[2, 3] Certain predisposing factors, including advanced age, smoking, and pre-existing cardiovascular conditions, significantly increase the risk of severe COVID-19 outcomes.[3,4] These factors contribute to higher disease progression rates and increased mortality, particularly in patients with multiple comorbidities. COVID-19 treatment with antiviral agents is guided by disease severity and the patient's risk of hospitalization or progression to severe illness, as outlined in the World Health Organization (WHO) and the Infectious Diseases Society of America (IDSA) guidelines.[4,5] Both guidelines recommend nirmatrelvir/ritonavir for patients with non-severe symptoms, mild to moderate disease, who are at high risk of progressing to severe COVID-19 or hospitalization.[4, 5]

Nirmatrelvir is a novel oral protease inhibitor that is active against M^{PRO}, which is a viral protease essential for viral replication.[6] Packaged with ritonavir, which is a potent CYP3A4 inhibitor and pharmacokinetic boosting agent, co-administered with ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range.[6] The Thai COVID-19 guidelines recommended nirmatrelvir/ritonavir as an oral antiviral agent for treating mild to moderate COVID-19 in adults at high risk of progression to severe disease, similar to the WHO and IDSA guidelines.[4, 5, 7] This treatment has reduced the risk of severe complications in symptomatic, high-

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risk adults with COVID-19.[7, 8]

However, the addition of ritonavir into the treatment regimen raises issues about potential drug–drug interactions (DDIs) due to its CYP3A4 inhibition. The patient's concurrent medications, including over-the-counter medicines, herbal supplements, and medication for underlying disease, need to be carefully reviewed before administering ritonavir-boosted nirmatrelvir to avoid serious drug interactions.[9] The majority of patients receiving nirmatrelvir/ritonavir are elderly or have underlying conditions, including diabetes mellitus, cardiovascular disease, chronic kidney disease, or immunocompromised status.[4, 5]

These patients frequently exhibit polypharmacy and are at high risk for drug interactions. Careful consideration of discontinuing or adjusting co-administered medications, particularly those administered to treat underlying conditions, is crucial and poses a significant challenge. However, data about the outcome and the management of drug interaction with nirmatrelvir/ritonavir in real-life practice are limited. This study aims to investigate the prevalence of potential drug interactions that occur when nirmatrelvir/ritonavir is prescribed for outpatient COVID-19. Additionally, we assess the drug-drug interaction management, the outcome of drug-drug interaction, 30 days hospitalization, 30 days mortality, and adverse drug events of nirmatrelvir/ritonavir.

METHODS

This retrospective study was conducted at King Chulalongkorn Memorial Hospital (KCMH), a 1479-bed tertiary referral and teaching hospital in Bangkok, Thailand. The inclusion criteria were (i) patients with mild to moderate COVID-19 at high risk for progression to severe disease who received at least one dose of nirmatrelvir/ritonavir from May 2022 to August 2022. High-risk criteria for the severe disease involved patients with the following comorbidities: age of ≥60 years, chronic obstructive pulmonary disease or other chronic lung diseases, chronic kidney disease (CKD) stage ≥3, cardiovascular disease, cerebrovascular disease, cancer (excluding those in remission), diabetes mellitus, obesity (weight of >90 kg or body mass index of ≥30 kg/m^2), cirrhosis (Child-Pugh class B or higher), immunocompromised conditions (e.g., undergoing chemotherapy, receiving immunosuppressive therapy, corticosteroids equivalent to ≥15 mg/day of prednisolone for ≥15 days), human immunodeficiency viruses infection with a CD4 cell count of <200 cells/mm^3[7] (ii) patients who received care at Outpatient Department. This study excluded patients who cannot be followed up by telephone during nirmatrelvir/ritonavir treatment, who did not know their underlying medications, who received inpatient care during nirmatrelvir/ritonavir treatment, who had suspected or confirmed nirmatrelvir/ritonavir allergy. The Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University, approved this study (IRB no. 0467/66).

Infectious disease pharmacists have implemented a protocol (Table S1) for physicians to use when prescribing nirmatrelvir/ritonavir, which is based on the Liverpool COVID-19 Drug Interactions Checker, at KCMH during the first phase of nirmatrelvir/ritonavir prescription for patients with COVID-19.[11] Physicians are encouraged to use the Liverpool COVID-19 Drug Interactions Checker or our protocol to evaluate DDIs between nirmatrelvir/ritonavir and co-administered medications before nirmatrelvir/ritonavir prescribing.[11]

Physicians use LEXIDRUG for checking DDIs in cases where the Liverpool COVID-19 DDI checker or our protocol does not include the medications of interest.[12] Infectious disease pharmacists reviewed patients' profiles who were receiving nirmatrelvir/ritonavir for treating COVID-19 by the e-PHIS-CUH program, using the pharmacist's recording form. This review included gathering demographic information, details on COVID-19 vaccination, age, underlying diseases, herbal or supplement used, BMI, kidney function, dosage, and data on concomitant medications. Pharmacists assessed the appropriateness of nirmatrelvir/ritonavir dosing using the United States Food and Drug Administration's dose recommendations and evaluated potential interactions with other medications taken alongside nirmatrelvir/ritonavir.[13] Pharmacists contacted patients by phone to ask about symptoms, medication adherence for nirmatrelvir/ritonavir, supplements or herbs, adverse events, and any recent hospitalizations after reviewing the patient's profile. They followed up with patients on days 2, 5, 10, and 30 after receiving nirmatrelvir/ritonavir. Pharmacists who identify any DDIs categorized as "should not be co-administered" in Liverpool or "avoid combination" in LEXIDRUG consulted with physicians to identify the need for dosage adjustments or medication discontinuation.[11, 12] Subsequently, physicians or nurses contacted patients to manage these DDIs. Figure 1 illustrates the flow of the pharmaceutical care for patients with COVID-19 who received nirmatrelvir/ritonavir.

Outcomes

Our study primarily aims to identify the prevalence of DDIs between nirmatrelvir/ritonavir and co-administration drugs. These interactions are categorized as "potentially clinically significant interaction" or "should not be co-administered" based on Liverpool Drug Interaction Checker assessments.[11] Alternatively, DDIs are classified as "consider therapy modification" or "avoid combination" if LEXIDRUG is utilized.[12] We classified the management for DDIs into two groups: intervention and observation. The observation group included patients with identified DDIs that were not managed by Liverpool COVID-19 Drug Interactions Checker, our protocol, or LEXIDRUG suggestions.[11, 12] The intervention group consisted of patients with DDIs that were actively managed through dose adjustments, use of alternative medications, or measures to avoid the interaction by Liverpool COVID-19 Drug Interactions Checker, our protocol, or LEXIDRUG suggestions.[11, 12] Serious adverse events caused by these interactions are defined as those resulting in disability, hospitalization, life-threatening situations, or death. Any other adverse events were considered minor.[14] Regarding other outcomes, we evaluated the rates of hospitalization and mortality within a 30-day after receiving nirmatrelvir/ritonavir, as well as monitored adverse drug events related to the use of nirmatrelvir/ritonavir. These adverse

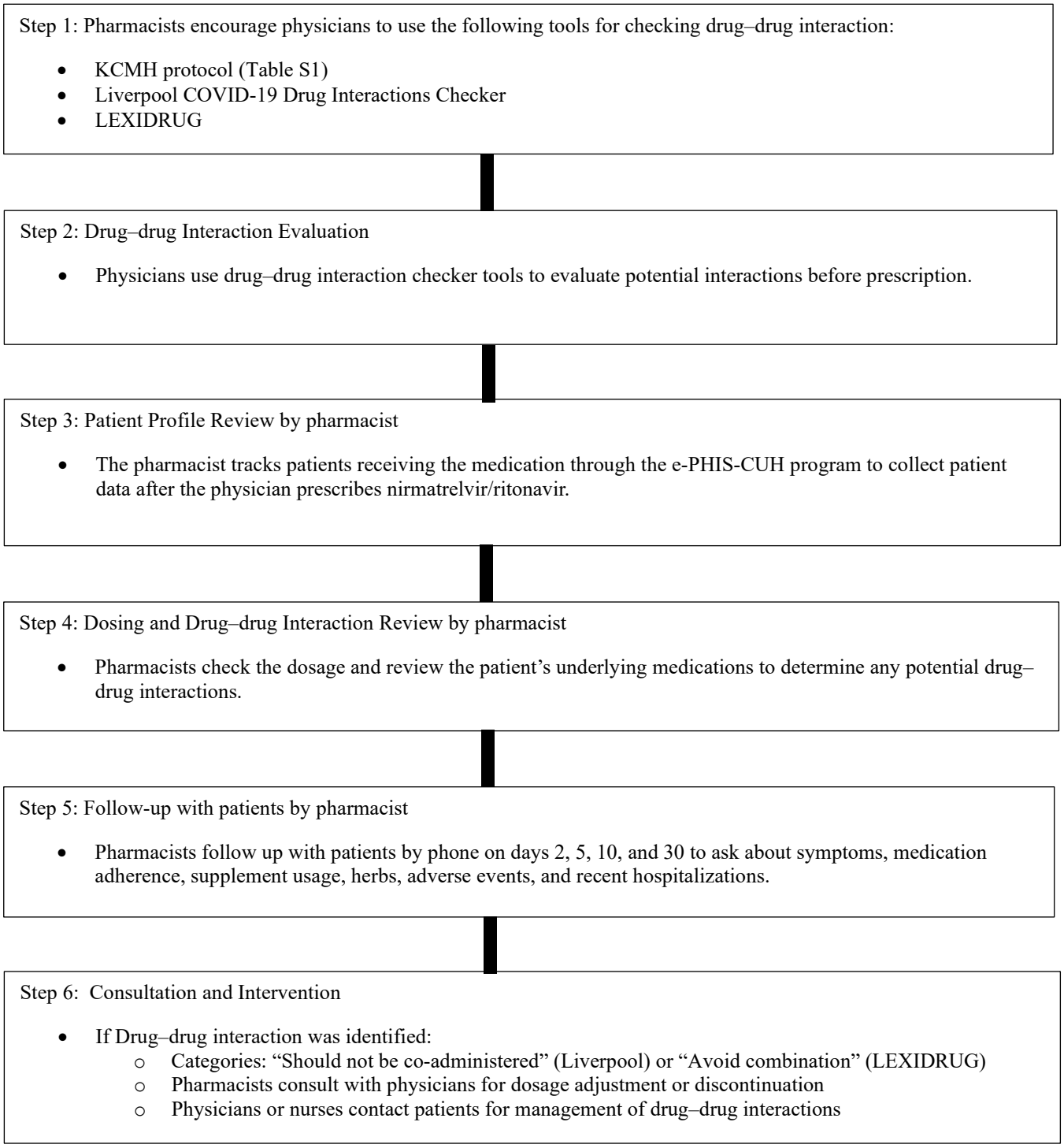

Figure 1. The flow of pharmaceutical care for patients with COVID-19 receiving nirmatrelvir/ritonavir At the Outpatient Department, King Chulalongkorn Memorial Hospital

events include dysgeusia, diarrhea, high blood pressure, and muscle aches.[6, 12]

Statistical analysis

Descriptive statistics were utilized to summarize the characteristics of our study population. Categorical variables, such as gender, underlying diseases, concomitant medications, and drug interactions were analyzed using frequencies and percentages. Continuous variables, including age and laboratory values, were reported as mean ± standard deviation (SD) for normally distributed data, or median with interquartile range (IQR) for non-normally distributed data. Comparisons between two categorical variables were conducted using the chi-square (χ^2) test. For continuous variables, independent t-tests were applied to compare mean values between two independent groups. The Shapiro-Wilk test was used to assess normality; if normality was not met, Mann-Whitney U test was employed. Variables with a *P*-value < 0.05 were considered statistically significant. All statistical analyses were performed using STATA (version 14.0).

RESULTS

Baseline characteristics of the study population

This study included 221 patients (Figure. 2). The median age was significantly higher in the DDI group (69 years) compared to the nonDDI group (63 years, $p < 0.005$). Underlying diseases were more prevalent in the DDI group, including hypertension (63.8% vs. 32.5%, $p < 0.005$), dyslipidemia (57.2% vs. 13.3%, $p < 0.005$), diabetes mellitus (44.2% vs. 18.1%, $p < 0.005$), cardiovascular disease (22.5% vs. 3.6%, $p < 0.005$), and CKD (23.2% vs. 3.6%, $p < 0.005$). Kidney function, assessed by estimated glomerular filtration rate (eGFR), was significantly lower in the DDI group, with more patients having eGFR of <30 ml/min/1.73 m² and requiring dialysis ($p < 0.005$). The dosage of nirmatrelvir/ritonavir significantly differed, with a higher proportion of the nonDDI group receiving the standard 300/100 mg dose every 12 h for 5 days compared to the DDI group (90.4% vs. 60.1%, $p < 0.005$). Treatment adherence was 99.5%. Table 1 shows the clinical characteristics of patients with COVID-19 in the DDI and nonDDI groups.

A total of 138 (62.4%) patients demonstrated at least one DDI. We determined 184 DDIs with nirmatrelvir/ritonavir. The drugs most predominantly involved in interactions with nirmatrelvir/ritonavir were simvastatin (32.6%), atorvastatin (28.3%), and manidipine (17.4%) (Figure. 3). Physicians detected and managed DDIs in 106 (57.6%) DDIs following the Liverpool COVID-19 Drug Interactions Checker, our protocol, or LEXIDRUG suggestions, with statins being the most prevalent group. Specifically, 50 (47.2%) involved simvastatin and 34 (32.1%) involved atorvastatin in the intervention group (Figure. 4). We revealed that calcium channel blockers were among the least managed medications for DDIs, with 25 (32.1%) involving manidipine and 6 (7.7%) involving lercanidipine (Figure. 4). No patients experienced serious adverse events from observed interactions, but we observed three patients who may have experienced minor adverse events related to these interactions (Table 2).

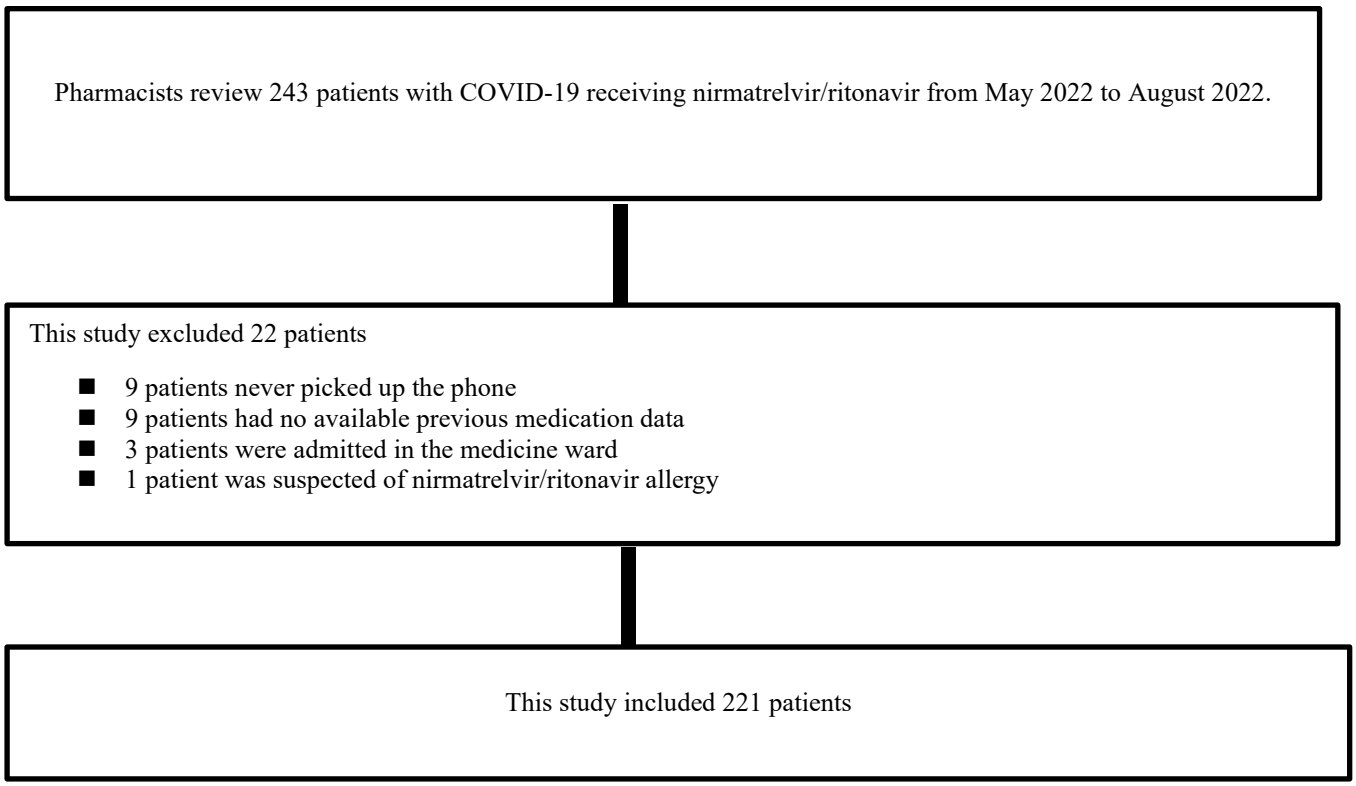

Figure 2. Flow diagram of the patient selection process in this study

Table 1. Clinical characteristics of patients with COVID-19 receiving nirmatrelvir/ritonavir from May 2022 to August 2022

	NonDDI (N = 83)	**DDI (N = 138)**	***P*-value**
Gender			
Female (%)*	56 (67.5)	85 (61.6)	0.232
Age (years), median (IQR)†	63 (49–72)	69 (62–79)	<0.005
Underlying disease*			
Hypertension	27 (32.5)	88 (63.8)	<0.005
Dyslipidemia	11 (13.3)	79 (57.2)	<0.005
Diabetes mellitus	15 (18.1)	61 (44.2)	<0.005
Cardiovascular disease	3 (3.6)	31 (22.5)	<0.005
Cancer	14 (16.9)	18 (13)	0.437
Chronic kidney disease	3 (3.6)	32 (23.2)	<0.005
Chronic liver disease	6 (7.2)	4 (2.9)	0.182
Others	13 (15.7)	24 (17.4)	0.853
Post COVID-19 vaccination (n = 201)*	**NonDDI* (N = 70)**	**DDI* (N = 131)**	***P*-value**
None	0	2 (1.5)	0.248
1 dose	0	0	
2 doses	5 (7.1)	12 (9.2)	
3 doses	43 (61.4)	71 (54.2)	
4 doses	20 (28.6)	46 (35.1)	
5 doses	2 (2.9)	0	
Kidney function test (n = 178)*	**NonDDI* (N = 50)**	**DDI* (N = 128)**	***P*-value**
eGFR of ≥60 ml/min/1.73 m^2	43 (86)	79 (61.7)	<0.005
eGFR of ≥30 to <60 ml/min/1.73 m^2	7 (14)	26 (20.3)	
eGFR of <30 ml/min/1.73 m^2	0	10 (7.8)	
Dialysis	0	13 (10.2)	
BMI (n = 177)*	**NonDDI* (N = 68)**	**DDI* (N = 109)**	***P*-value**
<30 kg/m^2	52 (76.5)	92 (84.4)	0.234
≥30 kg/m^2	16 (23.5)	17 (15.6)	
Herbal/supplement used (n = 141)*	**NonDDI* (N = 57)**	**DDI* (N = 84)**	***P*-value**
Yes	10 (17.5)	9 (10.7)	0.316
No	47 (82.5)	75 (89.3)	
Nirmatrelvir/ritonavir dosage*	**NonDDI* (N = 83)**	**DDI* (N = 138)**	***P*-value**
300/100 mg PO q 12 h × 5 days	75 (90.4)	83 (60.1)	<0.005
150/100 mg PO q 12 h × 5 days	6 (7.2)	23 (16.7)	
300/100 mg PO at day 1 then 150/100 mg PO OD × 5 days	2 (2.4)	32 (23.2)	

DDI = drug–drug interactions, BMI = body mass index, IQR = interquartile range, eGFR = estimated glomerular filtration rate, PO = Per Os, OD = once daily, ml = milliliter, m^2 = square meter
*Chi-square test, †Mann-Whitney U test

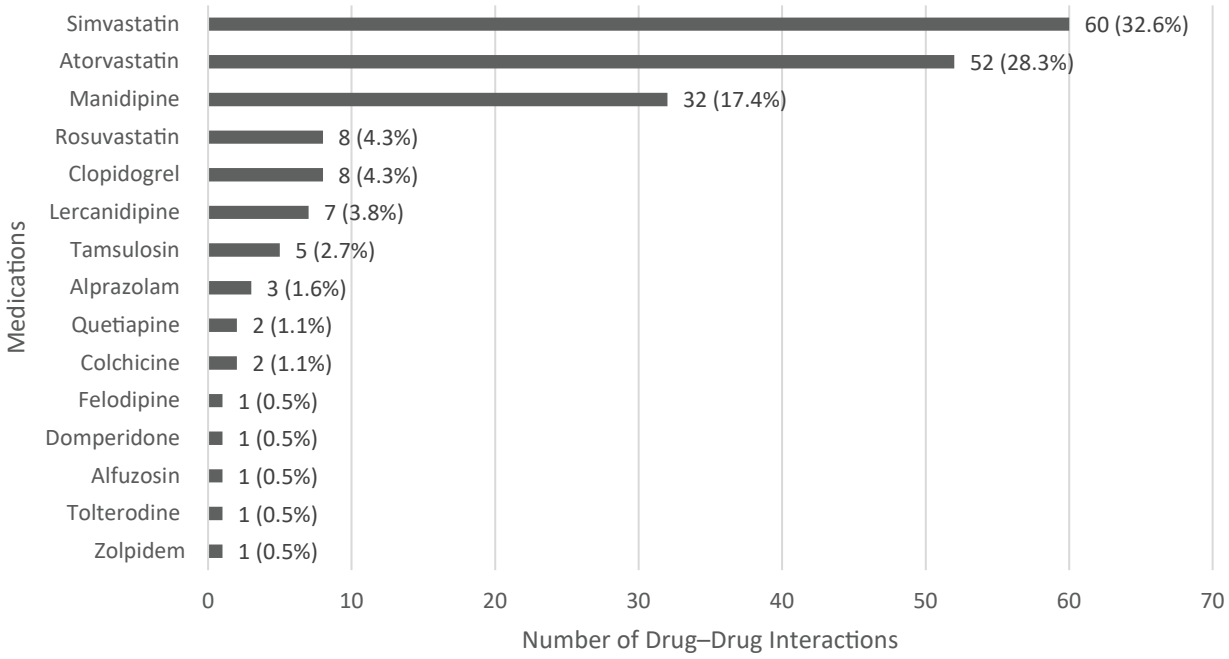

Figure 3. Number of DDIs with nirmatrelvir/ritonavir (n = 184)

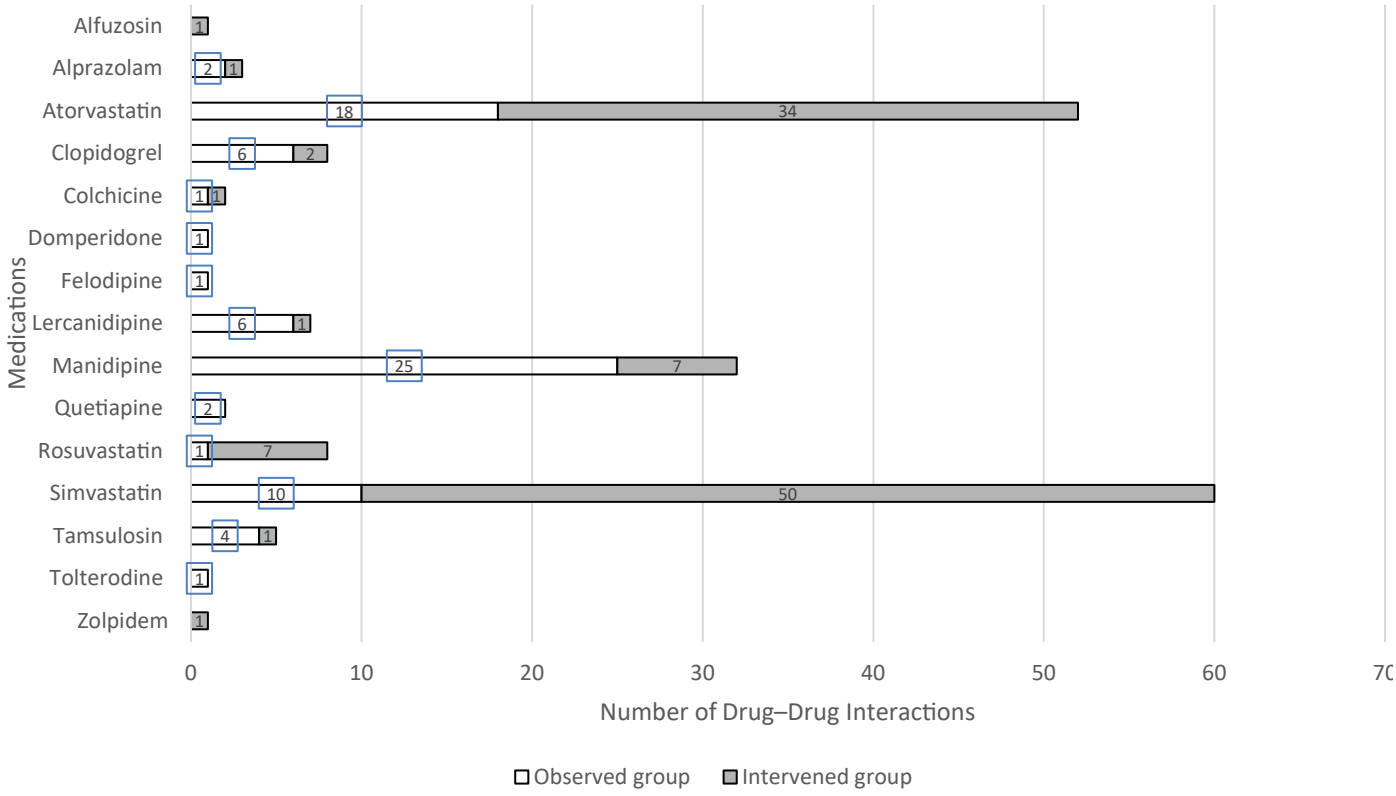

Figure 4. Number of observed (n = 78) and intervened (n = 106) drug–drug interactions in patients with COVID-19

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Table 2. Patients with observed drug–drug interactions and associated adverse events

Sex	Age	eGFR (CKD-EPI)	Nirmatrelvir/ ritonavir dosage	Drug–drug interaction (1)	Drug–drug interaction (2)	Symptoms	Onset of the symptoms	Management
Male	61 years	103 ml/min/ 1.73 m^2	Nirmatrelvir of 300 mg/ ritonavir of 100 mg BID	Manidipine	-	Dizziness	Day 5	Discontinued manidipine
Female	76 years	11.4 ml/min/ 1.73 m^2	Nirmatrelvir of 300 mg/ ritonavir of 100 mg OD on day 1 then Nirmatrelvir of 150 mg/ ritonavir of 100 mg OD	Manidipine	Atorvastatin	Headache	Day 5	Adverse event observed
Male	65 years	3 ml/min/ 1.73 m^2 (Hemodialysis)	Nirmatrelvir of 300 mg/ ritonavir of 100 mg OD on day 1 then Nirmatrelvir of 150 mg/ ritonavir of 100 mg OD	Manidipine	-	Dizziness, low blood pressure (90/60 mmHg)	Day 4	Discontinued manidipine

Pharmacists consulted with physicians in cases where the DDI is categorized as "should not be co-administered" in Liverpool or "avoid combination" in LEXIDRUG. Of these consultations, 13 resulted in the acceptance of recommendations to avoid using them together, including 6, 4, 2, and 1 cases involving lercanidipine, tamsulosin, simvastatin, and colchicine, respectively. All physicians agreed to discontinue co-administration of the drugs and to closely monitor the patients. However, none of the patients experienced serious adverse events due to these DDIs during our follow-up period.

All patients were followed up for hospitalization. We observed that 13 (5.9%) patients were admitted in terms of the causes of hospitalization in 30 days overall. None of the patients were hospitalized due to DDI outcomes. COVID-19 progression was observed in three patients. Three others were admitted for scheduled surgery. Two patients developed pneumonia following COVID-19, and one patient experienced septic shock with osteomyelitis. Another patient had a seizure triggered by COVID-19, while three additional patients were hospitalized for various treatments, including hemodialysis, kidney biopsy, and chemotherapy, respectively. Moreover, adverse events were detected in 130 (58.8%) patients, with dysgeusia being the most prevalent at 51.1%, followed by diarrhea and dizziness. Three patients experienced myalgia, which was not associated with DDIs with statins (Figure 5).

DISCUSSION

Our study revealed that 62.4% of the patients exhibited at least one pair of DDIs, similar to results from a MedSafer trial where 67.9% of patients were prescribed at least one interacting medication.[15] Among these interactions, simvastatin accounted for 32.6%, followed by atorvastatin at 28.3% and manidipine at 17.4%. Conversely, a previous study demonstrated that the most prevalent DDIs were with antithrombotic medications (37.4%), followed by statins (33.4%).[15] The discrepancy may be related to the differences in study populations. The previous study focused on hospitalized adults aged ≥65 years who were taking five or more medications, which may explain their higher prevalence of interactions with antithrombotic medications.[16] Additionally, approximately 35% of their patients demonstrated ischemic heart disease, a higher proportion than in our cohort, which could contribute to the increased interactions with antithrombotics.[16] Conversely, the frequency of interactions with statins in our study aligns with those in the previous study, caused by the common statin administration by physicians.[15, 16] These findings show that DDIs vary by patient characteristics, especially age, comorbidities, and polypharmacy. This highlights the need to consider these factors when assessing DDI risks in clinical practice.

An observational study evaluated the prevalence of potential DDIs (pDDIs) with ritonavir-containing COVID-19 therapy in adults with COVID-19.[17] This study revealed that 34.5% of patients were at risk of contraindicated or major pDDIs.[17] This prevalence was lower than in our study because this study included adults aged ≥18 years, with half of the patients being <60 years of age, which likely caused fewer comorbidities and fewer underlying medications that could result in DDIs.[17] Among the 718,387 patients assessed, the highest pDDI prevalence was observed with atorvastatin (12.5%) and amlodipine (9.5%), which are similar to our study.[17] However, we did not include amlodipine in our analysis because it is not categorized as a "potentially clinically significant interaction" or "should not be co-administered" based on the Liverpool Drug Interaction Checker.[11] Manidipine was classified as "consider therapy modification" in LEXIDRUG, which we used for guidance though not listed in the Liverpool database.[11, 12]

Another observational study evaluated patients hospitalized with a primary COVID-19 diagnosis who received direct-acting antivirals, including nirmatrelvir/ritonavir, and assessed the frequency of potential DDIs.[18] Similar to our study, approximately 52% of patients received medications categorized as "contraindicated" or "avoid concomitant use".[18] Notably, among the 788,238 patients, atorvastatin (29.1%) was the most predominant medication associated with DDIs, followed by tamsulosin (8%).[18] Our result align with these prior studies, confirming that statins are among the most frequently involved medications in DDIs.

The DDIs related to nirmatrelvir/ritonavir primarily come from ritonavir, popular for its role as a CYP3A and P-gp inhibitor.[9] Low-dose ritonavir was combined with nirmatrelvir to increase nirmatrelvir levels in the plasma by inhibiting CYP3A.[9] However, this interaction affects not only nirmatrelvir but also other medications. Consequently, DDIs that involve ritonavir-boosted nirmatrelvir may cause severe or life-threatening

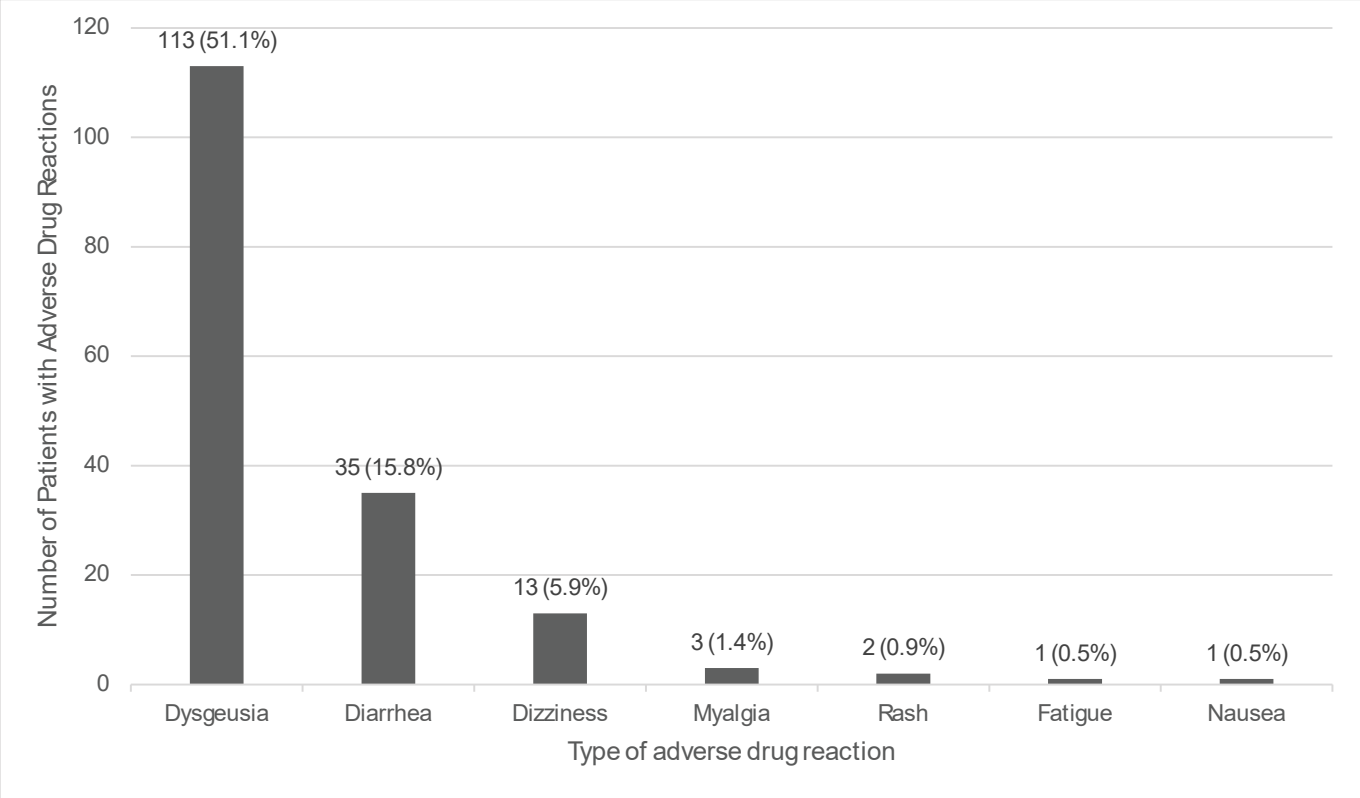

Figure 5. Number of Patients with Adverse Drug Reactions from nirmatrelvir/ritonavir (n = 221)

drug toxicities.[9] The lasting effect of ritonavir boosting after discontinuing a 5-day regimen is concerning. Ritonavir inhibits CYP3A through both reversible and irreversible mechanisms; thus, recovery from this inhibition after discontinuation depends partly on CYP3A4 regeneration. Consequently, the effects of ritonavir continued for several days after discontinuing the medication.[19] In particular, when nirmatrelvir/ritonavir is co-administered with simvastatin, simvastatin is not only required to be stopped while taking nirmatrelvir/ritonavir but must also be discontinued for an additional five days.[11]

The pharmacokinetic study of nirmatrelvir/ritonavir with midazolam and dabigatran demonstrated that nirmatrelvir/ritonavir increases the area under the curve $(AUC)_{inf}$ by nearly 14-fold with midazolam and by 1.9-fold with dabigatran.[20] Furthermore, ritonavir increased the AUC of amlodipine by 96% and rivaroxaban by 153%.[21, 22] A case report describes a patient who was hospitalized with rhabdomyolysis caused by a DDI between simvastatin and ritonavir, with ritonavir added one week before hospitalization.[23] Ritonavir not only increases the levels of other medications through DDIs, but we should also be aware of CYP inducer medications that decrease nirmatrelvir levels. The concentrations of nirmatrelvir/ritonavir were significantly reduced by strong inducers, potentially compromising its efficacy. Co-administration of nirmatrelvir/ritonavir with the strong inducer carbamazepine (300 mg twice daily) decreased nirmatrelvir AUC by 55.[13] DDIs with strong inducers cannot be prevented and require the use of an alternative COVID-19 treatment. Checking for drug interactions before starting nirmatrelvir/ritonavir is crucial.

Our study revealed that physicians determined and managed drug interactions in 106 (57.6%) prescriptions using our protocol. Among these, 50 (47.2%) involved simvastatin, and 34 (32.1%) involved atorvastatin. Interestingly, most of the drug interactions in the observation group in our study involved manidipine, clopidogrel, and lercanidipine, which have increased levels when co-administered with ritonavir. Manidipine is the leading observed medication for drug interactions, likely due to its absence from the Liverpool COVID-19 Drug Interactions website, although it is listed in the LEXIDRUG database.[11, 12] This discrepancy has caused some physicians, who relied solely on the Liverpool COVID-19 Drug Interactions Checker, to overlook the interaction between nirmatrelvir/ritonavir and manidipine. Different co-administrations with nirmatrelvir/ritonavir require different management approaches.

In particular, Liverpool recommends pausing atorvastatin during the treatment and restarting it three days after the last dose of nirmatrelvir/ritonavir if nirmatrelvir/ritonavir is co-administered with atorvastatin, due to the prolonged CYP3A4 inhibition by ritonavir.[11] Atorvastatin needs to be reduced to 10 mg daily, and the usual dose should be resumed three days after completing nirmatrelvir/ritonavir if co-administration

is necessary.[11] Unlike lercanidipine, which should be avoided and resumed three days after the last nirmatrelvir/ritonavir dose, it exerts no reduced dose option such as atorvastatin.[11] We have agreed to temporarily discontinue medications involved in drug interactions instead of reducing their dose to minimize confusion for physicians and patients. UpToDate recommends avoiding the concomitant use of nirmatrelvir/ritonavir for manidipine.[12] Increased manidipine effects and toxicities should be closely monitored. Alternatively, the dose needs to be reduced, although UpToDate does not specify the exact amount for the dosage reduction.[12] Physicians detect drug-drug interactions, but they may sometimes choose not to avoid or discontinue the medication if the benefits outweigh the risks. Surprisingly, none of the patients experienced serious side effects or fatalities during our close monitoring and phone follow-ups despite being exposed to these drug–drug interactions. However, we determined three patients in the observation group who subsequently experienced possible adverse events related to these interactions.

Hence, we recommend that healthcare professionals must check for interactions between nirmatrelvir/ritonavir and patients' co-medications due to the high drug–drug interactions prevalence, particularly in elderly patients with hypertension, dyslipidemia, diabetes, cardiovascular disease, and CKD. Physicians managed drug interactions in 106 (57.6%) prescriptions using our protocol. This indicates that healthcare professionals handle DDIs according to the suggested protocols without adverse events to patients. Additionally, our results revealed that administering the medications with close monitoring may be a viable approach if avoiding such drug interactions is not feasible. This strategy may be particularly applicable to calcium channel blockers, which were a common source of drug interactions in our study. Future research is warranted to focus on larger populations to assess the clinical outcomes and management strategies for other serious nirmatrelvir/ritonavir DDIs, such as those involving antiplatelet or antithrombotic drugs.

Pharmacovigilance studies indicated that the common side effects observed with nirmatrelvir/ritonavir are disease recurrence, dysgeusia, and diarrhea.[24, 25] Similarly, our study revealed that the most prevalent adverse events associated with nirmatrelvir/ritonavir are dysgeusia (51.1%), diarrhea (15.8%), and dizziness (5.9%).However, our study did not collect data on disease recurrence for patients who were not hospitalized. Our patients appear to experience a higher percentage of dysgeusia compared to those in other studies. Additionally, none of our patients were admitted because of the adverse drug events from nirmatrelvir/ritonavir. Nirmatrelvir/ritonavir is safe for COVID-19 patients, but healthcare professionals should inform them of common side effects like dysgeusia.

Our study had some strengths and limitations. This is the first study to assess real-life practice for drug interactions with nirmatrelvir/ritonavir, including prevalence, management type, and drug interaction outcomes. Additionally, we evaluated physicians' compliance with the protocol and outlined the management of drug interactions with nirmatrelvir/ritonavir and the pharmaceutical care for outpatients receiving this treatment. This study has several limitations. First, we measured outcomes only after implementing the protocol without obtaining baseline data before its implementation. This limits our ability to accurately evaluate the benefits of the protocol. Second, the Liverpool COVID-19 Interaction Checker and our protocol did not include some medications, causing undetected interactions. Third, the outcomes related to adverse drug reactions (ADRs) from drug interactions were primarily subjective, as they depended on patient self-reports and did not use an Adverse Drug Reaction Causality Assessment Tool to confirm whether the events were true ADRs. Follow-up was conducted via telepharmacy due to the isolation protocols for patients with COVID-19, which limited our ability to obtain objective outcomes and may have missed subclinical interactions. Fourth, the study may have included an insufficient number of patients to detect significant adverse events caused by these drug interactions. Lastly, some patients did not respond to phone calls on the final day of follow-up, which made it impossible to determine their hospital admission status.

CONCLUSION

Our research emphasizes the importance of assessing and managing potential drug interactions in patients with COVID-19 receiving nirmatrelvir/ritonavir. Establishing protocols for checking interactions before prescribing the medication and developing comprehensive monitoring strategies are crucial. These measures improve the safety and positive outcomes for this group of patients.

AUTHORS' CONTRIBUTION

Pongsakorn Charoenviwattanakij: conceptualization, data curation, formal analysis and writing- original draft. Chotirat Nakaranurack: conceptualization, methodology, supervision, writing- reviewing and editing. Wichai Santimaleeworagun: conceptualization, writing-review and editing, Watsa Charoenwaiyachet: conceptualization, writing-review and editing

CONFLICT OF INTEREST

All authors declare no conflict of interest.

References

1. Mahase E. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. BMJ. 2020;368:m1036.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382(13):1199-207.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
4. Agarwal A, Hunt BJ, Stegemann M, Rochwerg B, Lamontagne F, Siemieniuk RA, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379.
5. Bhimraj A, Morgan RL, Shumaker AH, Baden LR, Cheng VC-C, Edwards KM, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19 (September 2022). Clinical Infectious Diseases. 2022;78(7):e250-e349.
6. Lamb YN. Nirmatrelvir Plus Ritonavir: First Approval. Drugs. 2022;82(5):585-91.
7. Services DoM. Clinical Practice Guideline for COVID-19 [Internet]. Bangkok, Thailand2023 [cited 2024 sep 12]. 27:[Available from: https://covid19.dms.go.th/backend///Content//Content_File/Covid_Health/Attach/25660418150721PM_CPG_COVID-19_v.27_n_18042023.pdf.
8. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-408.
9. Marzolini C, Kuritzkes DR, Marra F, Boyle A, Gibbons S, Flexner C, et al. Recommendations for the Management of Drug-Drug Interactions Between the COVID-19 Antiviral Nirmatrelvir/Ritonavir (Paxlovid) and Comedications. Clin Pharmacol Ther. 2022;112(6):1191-200.
10. Adane ED, Herald M, Koura F. Pharmacokinetics of Vancomycin in Extremely Obese Patients with Suspected or Confirmed taphylococcus aureus Infections. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2015;35(2):127-39.
11. University of Liverpool. COVID-19 Drug Interactions Checkers [Internet]. Liverpool, UK: University of Liverpool; [cited 2024 June 11]. Available from: https://covid19-druginteractions.org/checker.
12. UpToDate. Drug interactions List [Internet]. Waktham, MA: Wolters Kluwer; [cited 2024 June, 11]. Available from: https://www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist.
13. U.S. Food and Drug Administration (FDA). Ritonavir-boosed nirmatrelvir (Paxlovid) [package insert]. U.S. Department of Health and Human Services; 2023 [cited 2024 Feb 20]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf.
14. U.S. Food and Drug Administration (FDA). What is a Serious Adverse Event? [Internet]. : U.S. Department of Health and Human Services; 2023 [cited 2024 April 30]. Available from: https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.
15. Ross SB, Bortolussi-Courval É, Hanula R, Lee TC, Goodwin Wilson M, McDonald EG. Drug Interactions With Nirmatrelvir-Ritonavir in Older Adults Using Multiple Medications. JAMA Netw Open. 2022;5(7):e2220184.
16. McDonald EG, Wu PE, Rashidi B, Wilson MG, Bortolussi-Courval É, Atique A, et al. The MedSafer Study—Electronic Decision Support for Deprescribing in Hospitalized Older Adults: A Cluster Randomized Clinical Trial. JAMA Internal Medicine. 2022;182(3):265-73.
17. Igho-Osagie E, Puenpatom A, Williams MG, Song Y, Yi D, Wang J, et al. Prevalence of potential drug-drug interactions with ritonavir-containing COVID-19 therapy. J Manag Care Spec Pharm. 2023;29(5):509-18.
18. Mozaffari E, Chandak A, Ustianowski A, Rivera CG, Ahuja N, Jiang H, et al. Prevalence of Potential Drug Interactions With Direct-Acting Antivirals for COVID-19 Among Hospitalized Patients. Clin Ther. 2024;46(10):778-84.
19. Ratain MJ, Greenblatt DJ. Drug Interactions With a Short Course of Nirmatrelvir and Ritonavir: Prescribers and Patients Beware. J Clin Pharmacol. 2022;62(8):925-7.
20. Cox DS, Rehman M, Khan T, Ginman K, Salageanu J, LaBadie RR, et al. Effects of nirmatrelvir/ritonavir on midazolam and dabigatran pharmacokinetics in healthy participants. Br J Clin Pharmacol. 2023;89(11):3352-63.
21. Courlet P, Guidi M, Alves Saldanha S, Cavassini M, Stoeckle M, Buclin T, et al. Population pharmacokinetic modelling to quantify the magnitude of drug-drug interactions between amlodipine and antiretroviral drugs. Eur J Clin Pharmacol. 2021;77(7):979-87.
22. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol. 2013;76(3):455-66.
23. Cheng CH, Miller C, Lowe C, Pearson VE. Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. Am J Health Syst Pharm. 2002;59(8):728-30.
24. Li M, Zhang QS, Liu XL, Wang HL, Liu W. Adverse Events Associated with Nirmatrelvir/Ritonavir: A Pharmacovigilance Analysis

Based on FAERS. Pharmaceuticals (Basel). 2022;15(12).
25. Pannu V, Udongwo N, Imburgio S, Johal A, Mararenko A, Pozdniakova H, et al. Adverse Events of SARS-CoV-2 Therapy: A Pharmacovigilance Study of the FAERS Database. Ann Pharmacother. 2024;58(2):105-9.

Table S1. KCMH protocol for Nirmatrelvir/ritonavir

Drug	**Nirmatrelvir/Ritonavir**					
Dosage form	**Paxlovid™** film coat tablet (Nirmatrelvir 150 mg/Ritonavir 100 mg)					
Dose	**Adult**					
	• Nirmatrelvir 300 mg with ritonavir 100 mg, taken twice daily for 5 days (a total of 3 tablets per dose).					
	• It should be taken within 5 days of symptom onset.					
	Children ≥ 12 years and adolescent, weighing ≥ 40 kg					
	• Nirmatrelvir 300 mg with ritonavir 100 mg, taken twice daily for 5 days (a total of 3 tablets per dose).					
	• It should be taken within 5 days of symptom onset.					
Dosage adjustment	**eGFR Based on CKD-EPI formulation**	**Dose**				
(BSA conversion in BMI > 35 kg/m² and BMI < 17 kg/m²)	**≥30 - < 60 mL/min**	Nirmatrelvir 150 mg with ritonavir 100 mg twice daily				
	<30 mL/min or Dialysis (weight ≥ 40 kg)	Nirmatrelvir 300 mg + ritonavir 100 mg both on day 1 then Nirmatrelvir 150 mg + ritonavir 100 mg once a day				
	Dialysis (weight < 40 kg)	Nirmatrelvir 150 mg + ritonavir 100 mg both on day 1 then Nirmatrelvir 150 mg + ritonavir 100 mg q 48 hr				
	Mild-moderate impairment (Child-Pugh class A or B): No dose adjustment					
	Severe hepatic impairment (Child-Pugh class C): Not recommended					
Administration	Oral: It is recommended to take the medication with or without food (the tablets should be swallowed whole; do not chew, crush, or break them).					
	• If you miss a dose and it's been less than 8 hours since your scheduled dose, take the missed dose as soon as you remember and take the next dose at the regular time.					
	• If you miss a dose and it's been more than 8 hours since your scheduled dose, skip the missed dose and take the next dose at the regular time.					
Major drug interaction	**Drug interactions that increase the concentration of co-administered medications ***Always check for drug interactions*****					
	Antiarrhythmic drugs	**Sedatives**	**Alpha-1 adrenoreceptor antagonists**:	**Anti-gout drugs:**	HMG-CoA reductase inhibitors:	**Ergot derivatives**
	Amiodarone	Clorazepate	Alfuzosin	Colchicine	Lovastatin	Dihydroergotamine
	Bepridil	Diazepam	**Analgesics:**	**Antipsychotics:**	Simvastatin	Ergonovine
	Dronedarone	Estazolam	Pethidine	Lurasidone	**Microsomal triglyceride transfer protein (MTTP) inhibitors:**	Ergotamine
	Flecainide	Flurazepam	**Anti-anginals:**	Pimozide	Lomitapide	Methylergonovine
	Propafenone	Triazolam	Ranolazine	Clozapine	**PDE5 inhibitors:**	
	Quinidine	Midazolam	**Antihypertensive:**	Quetiapine	Avanafil	
	Prokinetic drugs	**Anticancers**	Lercanidipine		Vardenafil	
	Cisapride	Neratinib			Sildenafil	
		Venetoclax				
	Drug interactions that decrease the concentration of Nirmatrelvir/Ritonavir ***Always check for drug interactions***					
	anticonvulsant	Antimycobacterial drugs				
	• Carbamazepine	• Rifampin				
	• Phenobarbital	• Rifapentine				
	• Phenytoin					
ADRs	Possible side effects include dysgeusia, diarrhea, and vomiting.					
Pregnancy	There is no information available about the use of Paxlovid during pregnancy. It is not recommended for use while pregnant.					

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Lactation	There is no data on the use of Paxlovid during breastfeeding. It is advised to discontinue breastfeeding for 7 days after the last dose of Paxlovid.
Precaution	• Hepatic transaminase elevation, hepatitis, jaundice
	• Hypersensitivity reaction
	• Renal impairment
	• Risk of HIV-1 protease inhibitor drug resistance
	• If the patient is already taking ritonavir from other medication regimens, it is not necessary to stop ritonavir; it can be used alongside Paxlovid.
Monitoring	Liver function test, Serum creatinine