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# POTENTIAL DRUG-DRUG INTERACTIONS AMONG U.S. ADULTS TREATED WITH NIRMATRELVIR/RITONAVIR: A CROSS-SECTIONAL STUDY OF THE NATIONAL COVID COHORT COLLABORATIVE (N3C)

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## Abstract

**Importance.—**Nirmatrelvir/ritonavir has potential to interact with many drugs.

**Objective.—**To estimate the prevalence of potential moderate to severe drug-drug interactions (DDIs) involving nirmatrelvir/ritonavir, identify interacting medications, and evaluate risk factors associated with potential DDIs.

**Design, Setting, and Participants.—**Cross-sectional study using electronic health records from the National COVID Cohort Collaborative Enclave, one of the largest COVID-19 data resources in the United States. Study participants were outpatients aged ≥18 years and started nirmatrelvir/ritonavir between December 23, 2021 and March 31, 2022.

**Main Outcome and Measures.—**Potential moderate to severe DDIs, defined as starting interacting medications reported by National Institutes of Health 30 days before or 10 days after starting nirmatrelvir/ritonavir.

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**Disclosures**: Dr. Alexander is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, for whom he has served as a paid expert witness; and is a past member of OptumRx's National P&T Committee. Dr. Garibaldi is a member of the FDA Pulmonary-Asthma Drug Advisory Committee and has received consulting fees from Janssen Research and Development LLC, Gilead Sciences and Atea Pharmaceuticals. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

**Ethics approval**: The Johns Hopkins Medicine Institutional Review Boards waived the requirement for informed consent and deemed work in the N3C Data Enclave to be exempt research.

**Results.—**Of 3214 outpatients who started nirmatrelvir/ritonavir, the mean age was 56.8±17.1 years, 39.5% were male, and 65.8% were non-Hispanic white. Overall, 521 (16.2%) were potentially exposed to at least one moderate to severe DDI, most commonly to atorvastatin (19.2% of all DDIs), hydrocodone (14.0%), or oxycodone (14.0%). After adjustment for covariates, potential DDIs were more likely among individuals who were older (odds ratio [OR] 1.16 per 10-year increase, 95% confidence interval [CI] 1.08-1.25), male (OR 1.36, CI 1.09-1.71), smokers (OR 1.38, CI 1.10-1.73), on more co-medications (OR 1.35, CI 1.31-1.39), and with a history of solid organ transplant (OR 3.63, CI 2.05-6.45).

**Conclusions and Relevance.—**One in six of individuals receiving nirmatrelvir/ritonavir were at risk of a potential moderate or severe DDI, underscoring the importance of clinical and pharmacy systems to mitigate such risks.

### Keywords

Drug interactions; drug safety; SARS-CoV-2; antivirals; patient safety; nirmatrelvir/ritonavir

## 1 INTRODUCTION

As of April 3, 2023, the COVID-19 pandemic has caused more than 104 million infections and 1,125,366 deaths in the United States.[1] Fortunately, a variety of effective antiviral therapies have been developed and brought to market since the pandemic started, including nirmatrelvir/ritonavir, an oral antiviral medication, approved through a U.S. Food and Drug Administration Emergency Use Authorization (EUA) for the treatment of mild to moderate COVID-19 disease on Dec 22, 2021.[2]

Despite its demonstrated efficacy at reducing COVID-19-related hospitalization or death among unvaccinated individuals, nirmatrelvir/ritonavir has well characterized drug-drug interactions (DDIs) with dozens of medicines because of its effect on drug metabolizing enzymes and drug transporters.[3 -9] Specifically, both nirmatrelvir and ritonavir are CYP3A (Cytochrome P450, family 3, subfamily A)substrates, so use of nirmatrelvir/ritonavir with drugs that are potent CYP3A inducers may reduce the efficacy of nirmatrelvir/ritonavir, such as with phenobarbital or carbamazepine. On the other hand, due to the strong CYP3A inhibition effect of ritonavir, taking nirmatrelvir/ritonavir with drugs that are metabolized by CYP3A enzymes may result in dangerously elevated levels of interacting drugs, such as with cyclosporine, quinidine, or atorvastatin. [5] Despite the theoretical risks of such events, there is relatively little known about how commonly potential moderate or severe DDI may occur with nirmatrelvir/ritonavir in the United States. A review, which synthesized the potential DDIs of various COVID-19 treatments from six drug interaction databases, claimed that taking nirmatrelvir/ritonavir and cardioprotective drugs together may increase the risk of bleeding, rhabdomyolysis, and myopathy. [10]

We conducted a cross-sectional study using electronic medical records from a large national cohort of individuals with COVID-19 to characterize the prevalence of potential moderate to severe DDIs among individuals receiving nirmatrelvir/ritonavir in the United States. In addition, we examined the sociodemographic and clinical characteristics of such individuals to understand who may be at higher risk of these potential adverse events.

# 2 METHODS

## 2.1 Data and Subjects

We used the National Covid Cohort Collaborative (N3C) Data Enclave, one of the largest COVID-19 clinical data resources supported by National Institutes of Health (NIH) in the United States.[11] Its detailed design and development are described in other places.[12] Briefly, N3C regularly collects up-to-date individual-level information from electronic health records of both COVID-19 patients and non-COVID controls. Original data including sociodemographic characteristics, clinical observations, drug prescription, and laboratory tests are then transferred into the Observational Medical Outcomes Partnership (OMOP) common data model and stored in this central, secured enclave.[12-13] More than 70 sites have contributed data to this enclave and 5.8 million COVID-19 cases have been captured.[14] Individual patient-level data in the limited data set was used to conduct our analyses. Adults (aged ≥18 years) from 28 sites who were prescribed nirmatrelvir/ritonavir once between Dec 23, 2021 and March 31, 2022 were included. Because nirmatrelvir/ritonavir is authorized for outpatient use and because of our interest in the prevalence and prevention of DDIs in ambulatory care, we excluded persons who were hospitalized 30 days before nirmatrelvir/ritonavir initiation (Figure 1)[15].

## 2.2 Definition of Drug-Drug Interaction

The N3C data includes information regarding when a given drug product was started, although the “start date” does not differentiate new prescriptions from refills, nor necessarily include every refill for a given medicine. [16] Using this information, we conservatively considered individuals who started or refilled an interacting medication, as identified by the NIH COVID 19 treatment guidelines, 30 days before or 10 days after starting nirmatrelvir/ritonavir (concomitant medication use period) as at risk for potential DDIs (eTable 1).[4] We added an extra 5 days after the 5-day nirmatrelvir/ritonavir treatment course to account for the remaining nirmatrelvir/ritonavir inhibiting effects.[4,17] In N3C, normalized medication identifiers and medication start date were clearly recorded while quantities, days of supply, or drug exposure end date were unavailable. Without information on treatment course, we were unable to tell if prescribed medications were taken simultaneously. Also, whether patients were asked to temporarily withhold or stop interacting drugs while taking nirmatrelvir/ritonavir was unknown. Therefore, we assumed that patients took prescribed medications continuously in the pre-specified concomitant medication use period and were potentially exposed to DDIs if offending medications were prescribed in this period.

## 2.3 Outcomes

Our main outcome was potential moderate to severe DDIs listed in the NIH COVID-19 treatment guideline.[4] The NIH categorized outpatient medications into five groups based on the likelihood and severity of the interaction with nirmatrelvir/ritonavir: (i) Medications Without Clinically Relevant Interactions, (ii) Continue Concomitant Medication and Monitor for Adverse Effects, (iii) Adjust Concomitant Medication Dose and Monitor for Adverse Effects, (iv) Temporarily Withhold Concomitant Medication If Clinically Appropriate, and (v) Prescribe Alternative COVID-19 Therapy. Nirmatrelvir/ritonavir users who were prescribed non-topical medications from one of the following categories were

potentially at risk for moderate to severe DDIs: (i) Adjust Concomitant Medication Dose and Monitor for Adverse Effects; (ii) Temporarily Withhold Concomitant Medication If Clinically Appropriate; and (iii) Prescribe Alternative COVID-19 Therapy (eTable 1).

### 2.4 Covariates

We included sociodemographic factors (age, gender, race and ethnicity, residency location) and clinical factors (BMI (Body Mass Index), smoking status, number of co-medications, disease diagnosis, Charlson comorbidity index) in our analysis. We categorized race and ethnicity into five levels: non-Hispanic white, non-Hispanic black, Hispanic and Latino, Other (American Indian and Alaska Native, non-Hispanic; Asian, non-Hispanic; Native Hawaiian and Other Pacific Islander, non-Hispanic; Other race, non-Hispanic), and missing race and ethnicity to avoid small number of participants in specific race and ethnicity group. We extracted all the disease diagnosis history before and on the day of nirmatrelvir/ritonavir prescription to characterize comorbidity. We calculated the Charlson comorbidity index, a validated summary measure of 17 diseases for each participant and then categorized the index into five mutually exclusive groups: score of 0, 1, 2, 3, and 4 or more[18]. We also included diagnosis of cardiovascular diseases, diabetes, and pulmonary disease as dichotomous covariates. We included all medications started in the concomitant medication use period except nirmatrelvir/ritonavir as co-medications. A medicine in its salt form or ester form was regarded as the same as the medication without salt or ester. An exceedingly small number of patients were prescribed prodrug and its metabolites at the same time, and we counted them separately.

### 2.5 Statistical Analyses

We characterized the overall cohort using percentage for categorical variables and mean with standard deviation (SD), or median with interquartile range (IQR) when appropriate, for continuous variables. In the primary analysis, we calculated prevalence of potential moderate to severe DDIs in the overall cohort. To identify commonly prescribed interacting medications among people who were potentially at risk for DDIs, we collapsed medication and its combination products. Next, we performed logistic regression to evaluate the risk factors associated with potential moderate to severe DDIs. A univariable logistic regression model was used first to explore the independent associations between different covariates and potential DDIs. Basic sociodemographic factors including age, gender, race and ethnicity as well as factors with a p-value $< 0.1$ in the univariable model were examined in the final multivariable model. We rescaled age by dividing the original age by 10 and modelled it as continuous variables in our analysis. We included a dummy variable to capture individuals with missing information about race or ethnicity. BMI and residency location were excluded because of substantial missing data. The crude and adjusted odds ratio (OR) and their 95% confidence intervals (CI) were calculated to describe the associations.

### 2.6 Sensitivity Analysis

We performed two sensitivity analyses to examine whether the results vary based on how we defined the length of concomitant medication use. First, we applied a stricter definition of concomitant use by considering medications prescribed 15 days before or 10 days

after nirmatrelvir/ritonavir start date as concomitant medications. Second, we extended the concomitant use period to 60 days before or 10 days after nirmatrelvir/ritonavir start date to do a less conservative analysis. In each sensitivity analysis, the period for non-hospitalization varies with the concomitant medication use period (eFigure 1). We fitted the final multivariable logistic model from the primary analysis to assess the association between risk factors and potential DDIs.

We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to conduct and report our study [19]. Data extraction was conducted using Spark SQL and statistical analysis was performed using R (version 3.5) in the N3C Data Enclave. The Johns Hopkins Medicine Institutional Review Boards waived the requirement for informed consent and deemed work in the N3C Data Enclave to be exempt research.

# 3 RESULTS

## 3.1 Characteristics of the Study Population

Of 3574 people who started nirmatrelvir/ritonavir between December 23, 2021 and March 31, 2022, 3351 received nirmatrelvir/ritonavir only once in the study period. After we further excluded hospitalized individuals (n=49) and individuals with missing age,gender, or age <18 years (n=88), we identified 3214 people eligible for analysis (Figure 2). Overall, the mean age was 56.8 years (SD 17.1), 39.5% were male, 65.8% were non-Hispanic White, 59.7% were non-smokers, and 70.4% were urban residents. The most common comorbidities were cardiovascular disease (53.8%), pulmonary disease (30.1%), and diabetes (26.2%). The median number of co-medications was two (IQR 0-3.0) (Table 1).

## 3.2 Medications Involved in Potential Moderate to Severe DDIs

Approximately one in six (16.2%) people were potentially exposed to moderate to severe DDIs. Among the 521 patients with potential DDIs, statins and opioids were two major drug classes implicated in such DDIs. Atorvastatin was found to be the most frequently prescribed co-medication among nirmatrelvir/ritonavir users (19.2%), followed by hydrocodone (14.0%), oxycodone (14.0%), rosuvastatin (8.6%), and trazodone (6.3%). Additionally, 5.4% of nirmatrelvir/ritonavir users with potential DDIs received tacrolimus (Figure 3).

## 3.3 Risk Factors Associated with Potential DDIs

Our multivariable regression model identified patient age, gender, smoking status, number of comedications, and history of solid organ transplant as independent risk factors of potential moderate to severe DDIs among outpatient nirmatrelvir/ritonavir users. Older adults had slightly higher odds of being potentially exposed to DDIs (OR 1.16, 95% CI 1.08-1.25 per 10-year increase). Males (OR 1.36, 95% CI 1.09-1.71), smokers (OR 1.38, 95% CI 1.10-1.73), and those on more co-medications (OR 1.35, 95% CI 1.31-1.39) were significantly more likely to be exposed to DDIs. In addition, individuals with a history of solid organ transplant had 3-fold higher odds (OR 3.63, 95% CI 2.05-6.45). However, compared with non-Hispanic whites, non-Hispanic blacks (OR 0.59, 95% CI 0.40-0.89) and

individuals from other race and ethnicity (OR 0.37, 95% CI 0.18-0.78) had significantly lower odds of developing potential DDIs (Figure 4).

### 3.4 Sensitivity Analyses

Our sensitivity analyses varying the definitions of concomitant medication use period (ie, shortened or extended) generated substantively similar findings as the primary analysis (eTable 2). The prevalence of potential occurrence of DDIs was 12.2% in the analysis with shortened concomitant medication use period and 22.2% after relaxing the co-medication definition (extended concomitant medication use period). In both analyses, older age, male gender, smoking, increasing number of co-medications, and history of solid organ transplant remained statistically significant. Participants with Charlson Comorbidity Index equal to 1 were more likely to be exposed to potential DDIs compared to those with an index of 0 in the extended concomitant medication use period, but not in the shortened concomitant medication use period.

## 4 DISCUSSION

We characterized potential DDIs and their risk factors among ambulatory U.S. adults treated with nirmatrelvir/ritonavir. About one in six (16.2%) had at least one moderate to severe potential DDI, usually due to co-prescribed statins or opioids. Advanced age, male gender, increasing number of co-medications, and history of solid organ transplant were associated with a greater risk of potential DDIs. Our results persisted in sensitivity analyses varying definitions of the concomitant medication use period. These findings are important because of how commonly nirmatrelvir/ritonavir is used to treat COVID-19 among ambulatory adults in the United States.

Our work extends other assessments of the risk of potential nirmatrelvir/ritonavir DDIs, which arise from the rapid and potent inhibition effect of ritonavir instead of induction effect. [9] For example, in an analysis of national prescription data from Denmark, the authors estimated the proportion of older adults at risk of DDIs with nirmatrelvir/ritonavir ranged from 0.7% to 32% across age and interacting drug groups.[20] In another assessment that theoretically exposed the trial cohort which included older, hospitalized adults with polypharmacy to nirmatrelvir/ritonavir, more than two-thirds of individuals (68%) were subject to potential DDIs with nirmatrelvir/ritonavir.[21] Since both studies reported the proportion of interacting drugs among all older people rather than real nirmatrelvir/ritonavir users to evaluate the prevalence of potential DDIs involving nirmatrelvir/ritonavir, the prevalence was likely underestimated.

We identified several sociodemographic and clinical characteristics that were significantly associated with potential DDIs including individuals who are older, male, and on multiple medications. Interestingly, tobacco use was also an independent risk factor of potential DDIs, in contrast with prior work that did not find such an association.[22,23] Such differences may arise in part from the nature of the DDIs of interest, including triggering drugs for nirmatrelvir/ritonavir DDIs, such as salmeterol, statins, and oxycodone, that may be more commonly used among smokers with comorbidities.[24] Similarly, our finding of a greater risk of potential DDIs among those with solid organ transplant likely reflects the

more common use of immunomodulating medications, such as tacrolimus, among these individuals.

Our results highlight the importance of educational efforts targeting patients and providers to ensure that both are aware of the non-trivial prevalence of potential nirmatrelvir/ritonavir DDIs. Since the risk of DDIs varies considerably across different socioeconomic and clinical subpopulations, such information can be used to target educational initiatives. In addition, the non-trivial risk of nirmatrelvir/ritonavir DDIs speaks to the value of automated systems, including drug interaction websites and software to forestall potential DDIs,[25] and contemporary electronic medical record platforms with functionalities to screen for potential DDIs and to advise prescribers of such at the point of prescribing.[26,27] Although a variety of algorithms have been developed to perform such reviews, accuracy and comprehensiveness of these automated systems varies.[10,28]

Though we relied on NIH COVID 19 guidelines to identify potential DDIs involving nirmatrelvir/ritonavir, these guidelines provide an incomplete list of potential offending drugs, since the interacting medications listed by NIH are mainly CYP3A4 substrates. Ritonavir is a weak inhibitor of CYP2D6 at boosting doses of 100 mg/d to 200 mg/d and also inhibits transporters P-glycoprotein (P-gp), organic anion transporting polypeptides (OATP), and breast cancer resistance protein (BCRP), which may result in increasing concentration of medications whose metabolism relies on those enzymes and transporters.[9] Such inhibition effects should not be ignored. Additionally, drug classes such as calcium channel blockers and kinase inhibitors are not included in the NIH COVID-19 treatment guideline and information regarding some drug classes, such as chemotherapeutic agents, is imprecise. Moreover, there may be misclassification of the severity of potential DDIs. For example, oral midazolam and alprazolam have similar pharmacokinetic properties but belong to different potential DDI severity groups according to the NIH guideline.

Our study also has other limitations and generates new questions. First, our data do not include information as to whether clinicians or pharmacists may have counselled patients to temporarily withhold or stop potentially interacting drugs, and thus we may overestimate the prevalence of potential DDIs. On the other hand, many individuals take over-the-counter drugs and dietary supplements that may potentially interact with nirmatrelvir/ritonavir and lead to underestimates of the DDIs in question.[29] Second, our estimates of potential DDIs are conservative, since we don’t capture medicines prescribed outside of the participating N3C institutions, nor do we capture medicines prescribed more than 30 days prior to nirmatrelvir/ritonavir receipt unless they were refilled during our defined exposure window. Third, the N3C, while the one of the largest COVID cohorts in the United States, represents the experience of academic health systems. Fourth, we examined potential DDIs; future work is needed to examine the prevalence and risk factors for actual adverse events arising from these potential DDIs. Fifth, our analyses reflect early experience with nirmatrelvir/ritonavir and there may be important secular trends in its use, and potential DDIs, over time.[13] Finally, we analysed the association between a limited set of patient-level characteristics and potential nirmatrelvir/ritonavir DDIs; further work might examine other factors including prescriber training and experience.

## 5 CONCLUSION

In a large and diverse cohort of outpatient U.S. adults treated with nirmatrelvir/ritonavir, one in six were at risk of a potential moderate or severe DDI, underscoring the importance of clinical and pharmacy systems to mitigate such risks.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

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Data Partners with Released Data

The following institutions whose data is released or pending:

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Pending: Arkansas Children's Hospital — UL1TR003107: UAMS Translational Research Institute • Baylor College of Medicine — None (Voluntary) • Children's Hospital of Philadelphia — UL1TR001878: Institute for Translational Medicine and Therapeutics • Cincinnati Children's Hospital Medical Center — UL1TR001425: Center for Clinical and Translational Science and Training • Emory University — UL1TR002378: Georgia Clinical and Translational Science Alliance • HonorHealth — None (Voluntary) • Loyola University Chicago — UL1TR002389: The Institute for Translational Medicine (ITM) • Medical College of Wisconsin — UL1TR001436: Clinical and Translational Science Institute of Southeast Wisconsin • MedStar Health Research Institute — UL1TR001409: The Georgetown-Howard Universities Center for Clinical and Translational Science (GHUCCTS) • MetroHealth — None (Voluntary) • Montana State University — U54GM115371: American Indian/Alaska Native CTR • NYU Langone Medical Center — UL1TR001445: Langone Health's Clinical and Translational Science Institute • Ochsner Medical Center — U54GM104940: Louisiana Clinical and Translational Science (LA CaTS) Center • Regenstrief Institute — UL1TR002529: Indiana Clinical and Translational Science Institute • Sanford Research — None (Voluntary) • Stanford University — UL1TR003142: Spectrum: The Stanford Center for Clinical and Translational Research and Education • The Rockefeller University — UL1TR001866: Center for Clinical and Translational Science • The Scripps Research Institute — UL1TR002550: Scripps Research Translational Institute • University of Florida — UL1TR001427: UF Clinical and Translational Science Institute • University of New Mexico Health Sciences Center — UL1TR001449: University of New Mexico Clinical and Translational Science Center • University of Texas Health Science Center at San Antonio — UL1TR002645: Institute for Integration of Medicine and Science • Yale New Haven Hospital — UL1TR001863: Yale Center for Clinical Investigation

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## Data availability:

The datasets generated during and/or analysed during the current study are available in the NCATS N3C Data Enclave, https://covid.cd2h.org/

## Code availability:

Code is available from Xuya Xiao

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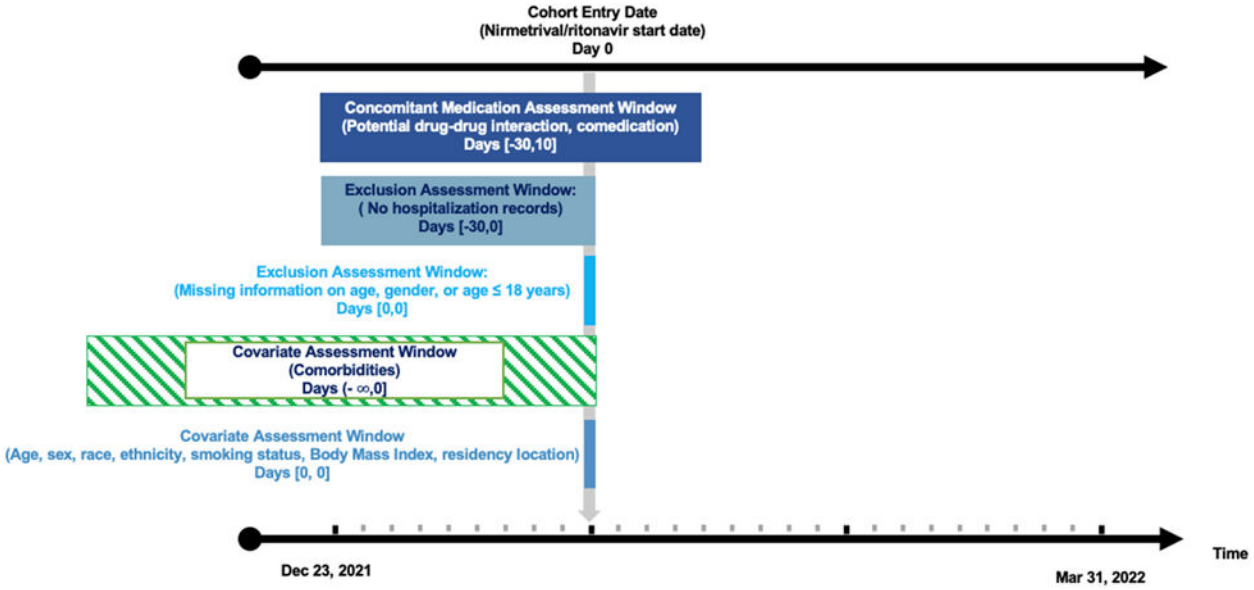


**Figure 1.**
Study implementation

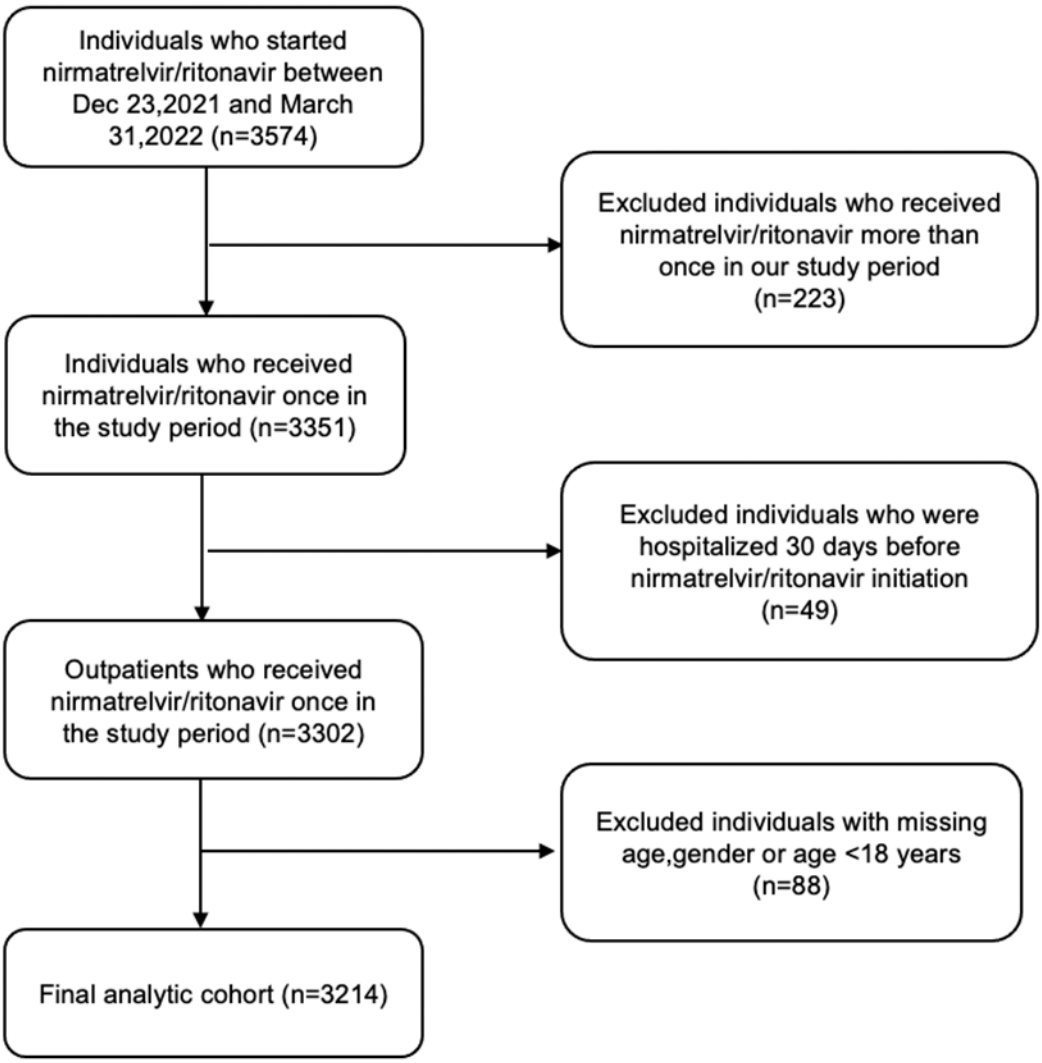


**Figure 2.**
Study participants flow diagram.

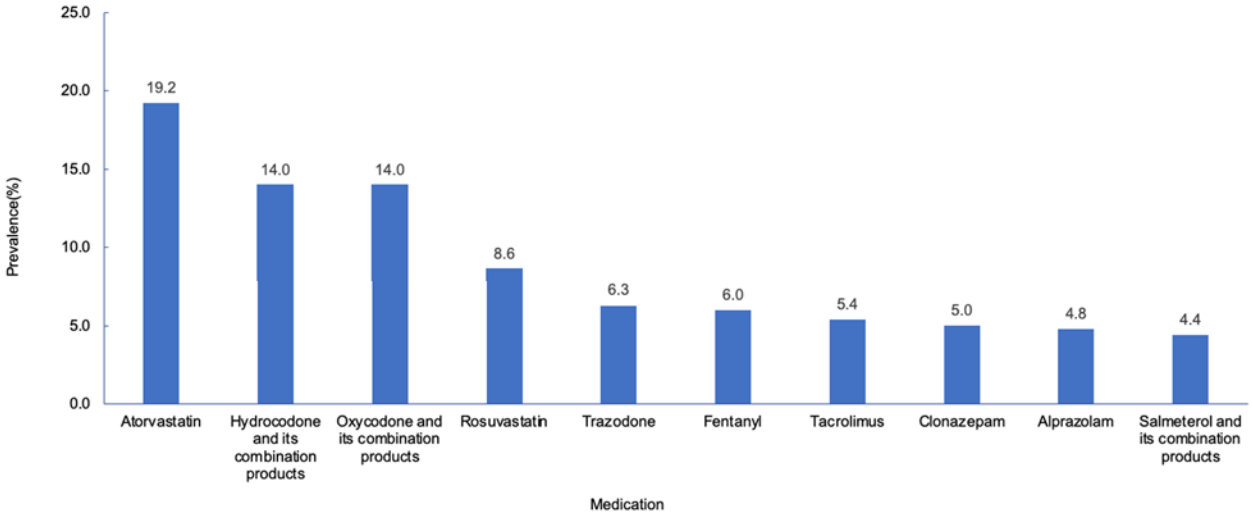


**Figure 3.**

Prevalence of most frequently prescribed co-medications among 521 individuals with potential moderate to severe DDIs

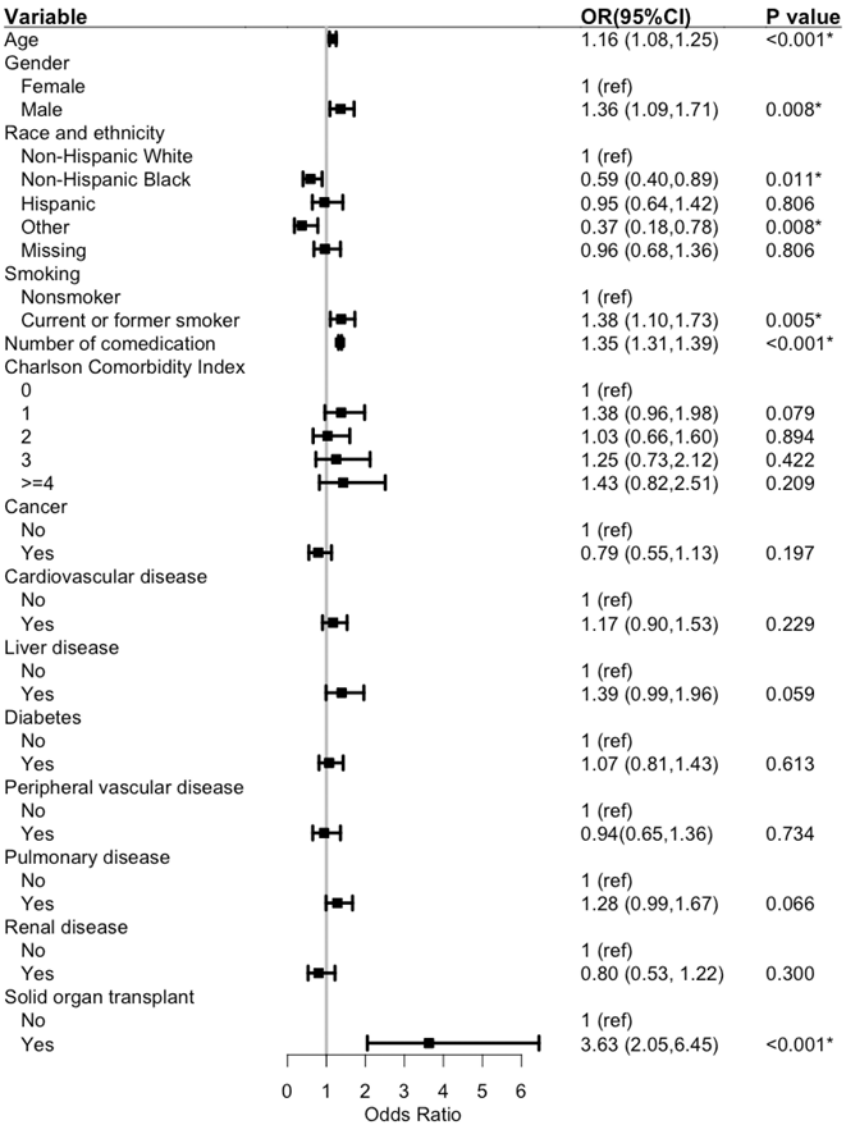


**Figure 4.**

Adjusted association between risk factors and potential moderate to severe DDIs

**DDIs** drug-drug interactions, **OR** odds ratio, **95%CI** 95% confidence interval

The p Value of rheumatic disease (p=0.115) was larger than 0.1 in univariable analysis and therefore not included in the multivariable model

*p Value is less than 0.05

**Table 1.**

Characteristics of the study population (n=3214 individuals)

| Characteristics | Total nirmatrelvir/ritonavir Users N= 3214 | Individuals without potential DDIs N= 2693 (83.8%) | Individuals with potential DDIs N=521 (16.2%) |
|---|---|---|---|
| Age, years, mean (SD) * | 56.8 (17.1) | 56.3 (17.3) | 59.4 (15.3) |
| Male gender (%) * | 39.5 | 38.2 | 46.1 |
| Race/ethnicity (%) * | | | |
| Non-Hispanic White | 65.8 | 65.7 | 66.6 |
| Non-Hispanic Black | 9.6 | 9.7 | 9.0 |
| Hispanic | 8.0 | 7.6 | 9.8 |
| †Other or missing | 16.6 | 17 | 14.6 |
| Body Mass Index (%) | | | |
| ≤25.0 kg/m$^2$ | 19.3 | 19.5 | 18.7 |
| 25.1-30.0 kg/m$^2$ | 20.6 | 21.0 | 18.4 |
| 30.1-40 kg/m$^2$ | 22.6 | 23.1 | 20.0 |
| ≥40.1 kg/m$^2$ | 9.5 | 9.5 | 9.4 |
| Missing | 28.0 | 27.0 | 33.6 |
| Smoking status (%) * | | | |
| Current or former smoker | 40.3 | 38.5 | 49.5 |
| Nonsmoker | 59.7 | 61.5 | 50.5 |
| Number of comedications, median (IQR) * | 2 (0-3.0) | 1.0 (0-3.0) | 5.0 (3.0-9.0) |
| Comorbidity (%) | | | |
| ‡Cardiovascular disease * | 53.8 | 51.2 | 67.0 |
| Diabetes * | 26.2 | 24.2 | 36.7 |
| Cancer * | 15.7 | 14.7 | 20.9 |
| Liver disease * | 10.4 | 9.2 | 16.5 |
| Peripheral vascular disease * | 9.7 | 8.6 | 15.4 |
| Pulmonary disease * | 30.1 | 27.9 | 41.3 |
| Rheumatic disease | 10.9 | 10.5 | 12.9 |
| Renal disease * | 8.8 | 7.7 | 14.4 |
| §Solid organ transplant * | 2.7 | 1.8 | 7.5 |
| Charlson Comorbidity Index,(%) * | | | |
| 0 | 31.3 | 34.1 | 16.9 |
| 1 | 24.8 | 25.0 | 23.8 |
| 2 | 15.6 | 15.5 | 15.7 |
| 3 | 8.5 | 8.1 | 10.4 |
| >= 4 | 19.8 | 17.3 | 33.2 |
| Residency location, (%) * | | | |

| Characteristics | Total nirmatrelvir/ritonavir Users N= 3214 | Individuals without potential DDIs N= 2693 (83.8%) | Individuals with potential DDIs N=521 (16.2%) |
|---|---|---|---|
| Urban | 70.4 | 71.3 | 66.0 |
| Rural | 9.6 | 9.9 | 8.3 |
| Missing | 19.9 | 18.8 | 25.7 |

**DDIs** drug-drug interactions**,SD** standard deviation, **IQR** interquartile range

†Other race and ethnicity includes American Indian and Alaska Native, non-Hispanic; Asian, non-Hispanic; Native Hawaiian and Other Pacific Islander, non-Hispanic; Other race, non-Hispanic.

‡Cardiovascular diseases include: coronary artery disease without myocardial infarction; myocardial infarction; congestive heart failure; hypertension; arrhythmia; stroke

§Solid organ transplant includes: lung transplant; heart transplant; liver transplant; kidney transplant; pancreas transplant

Percentage may not add up to 100% due to rounding error.

*$p<0.05$