Safety Assessment of Nirmatrelvir-Ritonavir in the FDA Adverse Event Reporting System: A Data Mining Approach

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BACKGROUND

- Nirmatrelvir-ritonavir, the first oral antiviral for the treatment of COVID-19, received approval in December 2021 by the Food and Drug Administration (FDA).
- There are significant concerns about the safety of this medication.
- The current drug safety data of nirmatrelvir-ritonavir are extremely limited because the clinical trial (EPIC-HR) leading to its approval had a small sample size (2,246 patients), strict exclusion and inclusion criteria (such as the inclusion criterion of "confirmed SARS-CoV-2 infection and symptom onset no more than 5 days before randomization" and exclusion criterion of "previous confirmed SARS-CoV-2 infection"), and thus some serious but rare adverse events may exist but has not been identified.[1]
- Little is known about gender or age disparities in the safety of nirmatrelvir-ritonavir.
- The FDA Adverse Event Reporting System (FARES) is a publicly available database maintained by the FDA.
- FAERS contains more than 28 million records and is used to support the FDA's post-marketing safety surveillance program, to monitor adverse drug events for drug and therapeutic biologic products.[2]

OBJECTIVE

- The objective of this study was to comprehensively evaluate the safety profile of nirmatrelvir-ritonavir using the FDA Adverse Event Reporting System (FAERS).

METHODS

Data source
- Data was sourced from the FDA Adverse Event Reporting System (FAERS).
- Data includes patient demographic information (age and sex), drug information (drug name, active ingredient, and route of administration), and reaction information through standardized preferred terms (PT).
- The adverse drug reaction data is made publicly available on a quarterly basis by the FDA.

Study design
- FAERS data from January 1, 2022 to December 31, 2023 were included in this study.
- If a report was submitted to the FDA multiple times with updated information, only the most recently submitted version was included in this study to avoid duplicate data.

Drug Exposure Definition
- Each drug was identified in FAERS by the medication's generic and brand names listed in the Drugs@FDA Database.

Reporting Odds Ratio (ROR)
- Reporting Odds Ratios and corresponding 95% confidence intervals (95% CI) were calculated for the association between nirmatrelvir-ritonavir and its adverse drug reactions (ADRs).
- ROR was calculated as the ratio of the odds of reporting an adverse event versus all other events for a given drug compared with the reporting odds for other drugs present in FAERS.
- An association was considered to be statistically significant when the lower limit of the 95%CI was greater than 1.

Subgroup analysis
- RORs for ADRs of nirmatrelvir-ritonavir among male and female patients were calculated.
- RORs for ADRs of nirmatrelvir-ritonavir among patients less than 65 years old and patients 65 years old or older were calculated.

Statistical software
- Microsoft Excel Office 365
- SAS 9.4

RESULTS

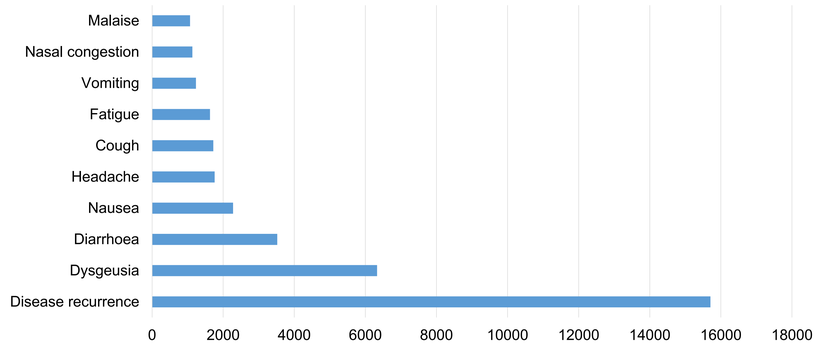

Figure 1. Number of reports for the top ten ADRs of nirmatrelvir-ritonavir.

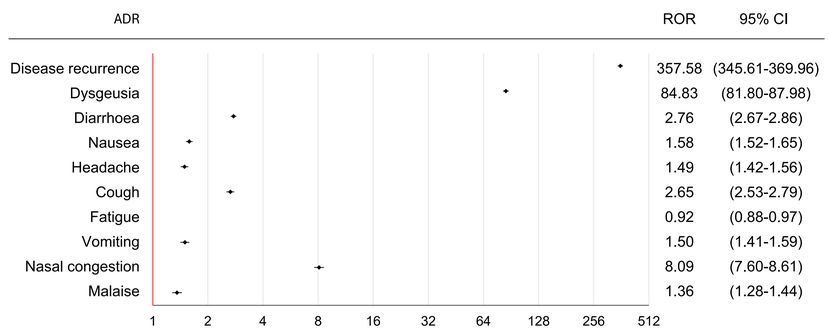

Figure 2. Reporting odds ratios for the top ten ADRs of nirmatrelvir-ritonavir.

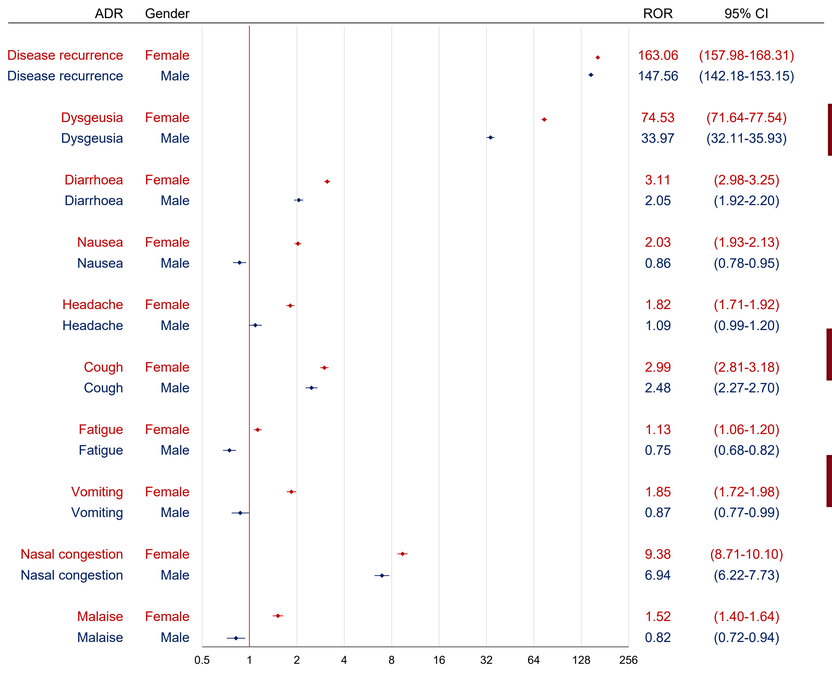

Figure 3. Reporting odds ratios for the top ten ADRs of nirmatrelvir-ritonavir by gender.

RESULTS

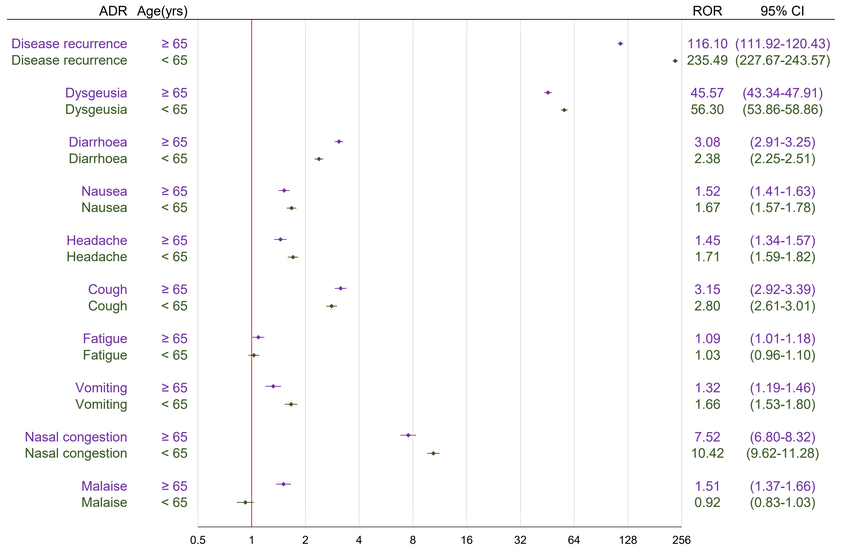

Figure 4. Reporting odds ratios for the top ten ADRs of nirmatrelvir-ritonavir by age.

- A total of 3,116,844 reports were considered, after inclusion criteria were applied.
- Nirmatrelvir-ritonavir had 42,751 reports.
- The top ten adverse drug reactions of nirmatrelvir-ritonavir (number of reports) were disease recurrence (15,707), dysgeusia (6,329), diarrhoea (3,520), nausea (2,277), headache (1,761), cough (1,722), fatigue (1,628), vomiting (1,233), nasal congestion (1,133), and malaise (1,069).
- RORs (95% CI) for these adverse drug reactions of nirmatrelvir-ritonavir were: disease recurrence 357.58 (345.61-369.96), dysgeusia 84.83 (81.80-87.98), diarrhoea 2.76 (2.67-2.86), nausea 1.58 (1.52-1.65), headache 1.49 (1.42-1.56), cough 2.65 (2.53-2.79), fatigue 0.92 (0.88-0.97), vomiting 1.50 (1.41-1.59), nasal congestion 8.09 (7.60-8.61), and malaise 1.36 (1.28-1.44).

CONCLUSIONS

- The top ten adverse drug reactions of nirmatrelvir-ritonavir were disease recurrence, dysgeusia, diarrhoea, nausea, headache, cough, fatigue, vomiting, nasal congestion, and malaise.
- Disease recurrence had the highest reporting association with nirmatrelvir-ritonavir.
- The findings of the project will aid clinicians and pharmacists when prescribing nirmatrelvir-ritonavir.

FUNDING

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REFERENCES

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2. United States Food and Drug Administration. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). Available from https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Accessed April 24, 2024.