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Effectiveness and Adverse Events of Nirmatrelvir/Ritonavir Versus Molnupiravir for COVID-19 in Outpatient Setting: Multicenter Prospective Observational Study

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ABSTRACT

Background: In this study, we aimed to compare the effectiveness and adverse reactions of nirmatrelvir/ritonavir and molnupiravir in high-risk outpatients with coronavirus disease 2019 (COVID-19).
Methods: This multicenter prospective observational study evaluated the rate of hospitalization, death, and adverse events within 28 days of oral antiviral agent prescription (molnupiravir, n = 240; nirmatrelvir/ritonavir, n = 240) to 480 nonhospitalized adult patients with COVID-19 from August 2, 2022 to March 31, 2023.
Results: Patients receiving molnupiravir had a higher prevalence of comorbidities (85.8% vs. 70.4%; $P < 0.001$) and a higher Charlson comorbidity index (2.8 ± 1.4 vs. 2.5 ± 1.5; $P = 0.009$) than those receiving nirmatrelvir/ritonavir. Three patients required hospitalization (nirmatrelvir/ritonavir group, n = 1 [0.4%]; molnupiravir group, n = 2 [0.8%]; $P = 1.000$). Nirmatrelvir/ritonavir was associated with a higher risk of adverse events than molnupiravir (odds ratio [OR], 1.96; 95% confidence interval [CI], 1.27–3.03), especially for patients aged 65 years and older (OR, 3.04; 95% CI, 1.71–5.39). The severity of adverse events in both groups was mild to moderate and improved after discontinuation of medication. In the molnupiravir group, age ≥ 65 years (OR, 0.43 95% CI, 0.22–0.86) and appropriate vaccination (OR, 0.37; 95% CI, 0.15–0.91) reduced the occurrence of adverse events.
Conclusion: The rates of hospitalization and death were low and not significantly different between high-risk patients who received either nirmatrelvir/ritonavir or molnupiravir. Although adverse events were more frequent with nirmatrelvir/ritonavir than with molnupiravir, none were severe. Nirmatrelvir/ritonavir can be safely used to treat COVID-19, while molnupiravir could be considered as an alternative treatment option for high-risk groups.

Keywords: COVID-19; Nirmatrelvir and Ritonavir Drug Combination; Molnupiravir

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The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Lee J. Data curation: Jung E, Kim YK. Formal analysis: Park JJ. Funding acquisition: Lee J. Investigation: Kim H, Lee SS. Methodology: Lee JS, Jung E, Park JJ. Software: Park JJ. Validation: Kim YK. Writing - original draft: Park JJ. Writing - review & editing: Jung E, Lee J.

INTRODUCTION

Since the first confirmed case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Wuhan in December 2019, there have been 761 million confirmed cases and 6.88 million deaths worldwide over a 3-year period.[1] However, the development of vaccines and treatments has markedly reduced the number of deaths and severe illness.[1,2]

The primary treatment for coronavirus disease 2019 (COVID-19) is the combination of nirmatrelvir and ritonavir; whereas molnupiravir is used as an alternative treatment for high-risk patients in the United States.[3] In the EPIC-HR trial, which assessed unvaccinated outpatients with mild-to-moderate COVID-19 and their risk factors, administration of nirmatrelvir/ritonavir led to an 89.1% reduction in COVID-19-related hospitalizations and deaths.[4] However, the effectiveness of this drug combination is limited because of the drug–drug interactions of ritonavir. By contrast, molnupiravir significantly reduced the risk of COVID-19-related hospitalization and death in the MOVe-OUT trial.[5] Unlike nirmatrelvir/ritonavir, molnupiravir does not interact with other drugs and can be used irrespective of renal function deterioration.

As the proportion of vaccinated individuals in the population increases and new variants of SARS-CoV-2 emerge, it is crucial to collect data on oral treatments that go beyond those obtained from clinical trials. Numerous studies have reported on the effectiveness and tolerability of nirmatrelvir/ritonavir and molnupiravir in real-world settings, particularly during periods when the omicron variant was prevalent.[6-10] These studies have indicated the effectiveness of nirmatrelvir/ritonavir and molnupiravir with no significant adverse events. However, most of these studies were conducted retrospectively.

In Korea, nirmatrelvir/ritonavir and molnupiravir received emergency approval from the Ministry of Food and Drug Safety in December 2021 and March 2022, respectively, as COVID-19 treatment regimens.[11] Nevertheless, there is a lack of data regarding their effectiveness and potential adverse events in the Korean population, where the mortality rate has been lower than that in other countries. Therefore, in this prospective study, we aimed to compare the effectiveness and adverse events of nirmatrelvir/ritonavir and molnupiravir, with the overarching goal of enhancing the preparedness of healthcare systems for future COVID-19 outbreaks.

METHODS

Study design

This prospective cohort study was conducted from August 2, 2022 to March 31, 2023, at 5 hospitals and 10 clinics in Korea. The study included patients aged 18 years and older who were diagnosed with COVID-19 by reverse transcription polymerase chain reaction or rapid antigen testing using a nasopharyngeal swab. These patients were then prescribed oral antiviral agents in an outpatient clinic.

Study population and treatment exposure

All patients diagnosed with COVID-19 underwent eligibility screening by physicians at each hospital. Following the guidelines for COVID-19 treatment provided by the Korean Centers for Disease Control and Prevention[12] (**Supplementary Data 1**), physicians prescribed the appropriate oral antiviral agent, that is, either nirmatrelvir/ritonavir or molnupiravir. Patients

who provided informed consent on the day of oral antiviral agent administration were included in this study.

A dose of 300/100 mg of nirmatrelvir/ritonavir or 800 mg of molnupiravir was administered twice daily for 5 days. A reduced dose of 150/100 mg of nirmatrelvir/ritonavir was administered twice daily for 5 days to patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/m^2. Nirmatrelvir/ritonavir was contraindicated in patients with an eGFR lower than 30 mL/min/m^2, and molnupiravir was used instead.

Data collection

The study collected data on various patient characteristics, including age, sex, height, weight, date of symptom onset, COVID-19 vaccination history, comorbidities, Charlson comorbidity index, date of COVID-19 diagnosis, stage of COVID-19 at diagnosis (mild or moderate), and body mass index (calculated using weight and height measurements). Patients were followed up for 28 days after the prescription of oral antiviral agents. The study team contacted patients by telephone on days 1, 2, 3, 4, 5, 6, 7, 14, and 28 after the prescription date to gather information on COVID-19 symptoms, adverse reactions to oral antiviral agents, discontinuation of antiviral agents, hospitalization, and death related to COVID-19. Cases where existing symptoms persisted or worsened were excluded from the estimation of adverse events attributed to oral antiviral agents. The study also categorized the COVID-19 vaccination history of patients as appropriate (≥ 2 vaccinations within 14–180 days of the last vaccination) or inappropriate (not vaccinated or only received one vaccination). If the oral antiviral agent was discontinued, the reason for the discontinuation was investigated. Hospitalization resulting from the progression of COVID-19 symptoms was considered as COVID-19-related hospitalization.

Study outcomes

The primary objective of the study was to assess hospitalization or death resulting from COVID-19 within 28 days following the prescription of oral antiviral agents. The secondary objectives included evaluating any adverse events and identifying the risk factors associated with adverse events and hospitalization. Adverse events were classified as mild, moderate, and severe. Briefly, mild: mild or transient discomfort, not requiring intervention or treatment; moderate: sufficiently discomforting to limit or interfere with daily activities, may require interventional treatment; and severe: significant symptoms that prevent normal daily activities, may require hospitalization or invasive intervention. Study outcomes were further analyzed following the classification of patients to two age groups: under 65 years and 65 years and older.

Statistical analysis

Categorical variables were compared using the χ^2 test and Fisher's exact test, whereas noncategorical variables were compared using the two-sided unpaired *t*-test or Mann-Whitney *U* test. Univariable and multivariable logistic regression analysis was performed to determine factors associated with hospital admission and adverse reactions. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the R software (R Foundation, Vienna, Austria).

Ethics statement

This study received approval from the Institutional Review Board (IRB) of Kangnam Sacred Heart Hospital (IRB No. 2022-05-038) and the Public Institutional Board designated by the Ministry of Health and Welfare (P01-202210-01-006). All patients provided written informed consent.

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RESULTS

Baseline characteristics

Of the 482 patients who provided informed consent, 2 individuals chose not to take the oral antiviral agents and withdrew from the study. Ultimately, the analysis included 480 patients, with all of them completing the duration of the study. Among the study population, 43.8% (n = 210) of patients were men; the mean age of patients was 67.2 (standard deviation, 10.1) years (**Table 1**). Molnupiravir and nirmatrelvir/ritonavir were prescribed to 240 (50.0%) patients, respectively. Among the participants, two had moderate symptoms, whereas the rest experienced mild symptoms at diagnosis. Comorbidities were documented in 375 (75.6%) patients, with their prevalence being significantly higher in the molnupiravir group than in the nirmatrelvir/ritonavir group (85.8% vs. 70.4%; $P < 0.001$). The Charlson comorbidity index was significantly higher in the molnupiravir group than in the nirmatrelvir/ritonavir group (2.8 ± 1.4 vs. 2.5 ± 1.5; $P = 0.009$). The majority of patients (89.4%) had received three or more doses of the COVID-19 vaccine. However, the rate of appropriate vaccination was 30.0% (n = 72) and 32.9% (n = 79) in the molnupiravir and nirmatrelvir/ritonavir groups, respectively ($P = 0.555$). The median time from symptom onset to the administration of oral antiviral agents

Table 1. Baseline characteristics of the study population (N = 480)

Characteristics	Total (N = 480)	Nirmatrelvir/Ritonavir (n = 240)	Molnupiravir (n = 240)	*P* value
Sex				0.927
Men	210 (45.8)	104 (43.3)	106 (44.2)	
Women	270 (54.2)	136 (56.7)	134 (55.8)	
Age, yr	67.2 ± 10.1	65.8 ± 10.2	68.6 ± 9.9	0.003
< 65	177 (36.9)	108 (45.0)	69 (28.8)	< 0.001
≥ 65	303 (63.1)	132 (55.0)	171 (71.2)	
Body mass index, kg/m^2	23.8 ± 3.4	23.6 ± 3.4	23.9 ± 3.3	0.270
Time from symptom onset, days	1 (1–2)	1 (1–2)	1 (1–2)	0.621
No. of comorbidities				0.001
0–1	363 (75.6)	198 (82.5)	165 (68.8)	
≥ 2	117 (24.4)	42 (17.5)	75 (31.2)	
Comorbidities	375 (78.1)	169 (70.4)	206 (85.8)	< 0.001
Hypertension	221 (46.0)	94 (39.2)	127 (52.9)	0.003
Diabetes mellitus	110 (22.9)	46 (19.2)	64 (26.7)	0.065
Cardiovascular disease	40 (8.3)	14 (5.8)	26 (10.8)	0.069
Cerebrovascular disease	8 (1.7)	2 (0.8)	6 (2.5)	0.285
Chronic lung disease	14 (2.9)	9 (3.8)	5 (2.1)	0.416
Solid tumor	25 (5.2)	14 (5.8)	11 (4.6)	0.681
Chronic kidney disease	7 (1.5)	1 (0.4)	6 (2.5)	0.128
Autoimmune disease	10 (2.1)	2 (0.8)	8 (3.3)	0.110
Charlson comorbidity index	2.7 ± 1.3	2.5 ± 1.2	2.8 ± 1.4	0.009
No. of vaccinations				0.001
0–1	15 (3.1)	3 (1.2)	12 (5.0)	
2	36 (7.5)	23 (9.6)	13 (5.3)	
≥ 3	429 (89.4)	214 (89.2)	215 (89.6)	
Times from last vaccination[a], days	262 (160–352)	263 (154–360)	263 (154–360)	0.343
Appropriate vaccination	151 (31.5)	79 (32.9)	72 (30.0)	0.555
Symptoms over 7 days[b]	220 (47.8)	106 (45.9)	114 (49.8)	0.455
Sputum	131 (28.5)	63 (27.3)	68 (29.7)	0.606
Cough	120 (26.1)	65 (28.1)	55 (24.0)	0.340
Sore throat	37 (8.0)	19 (8.2)	18 (7.9)	1.000
Symptoms over 28 days[b]	66 (14.3)	34 (14.7)	32 (14.0)	0.894
Cough	39 (8.5)	20 (8.7)	19 (8.3)	0.934
Sputum	17 (3.7)	8 (3.5)	9 (3.9)	0.716

Values are presented as number (%), mean ± standard deviation or median (interquartile range).
[a]Data analysis excluded participants who did not complete vaccination (n = 465).
[b]Data analysis excluded participants who discontinued oral antiviral agents (n = 460).

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was 1 day in both groups (P = 0.621). No significant differences were observed between the nirmatrelvir/ritonavir and molnupiravir groups regarding patients experiencing symptoms for 7 or more days and 28 or more days after starting the oral antiviral agents, respectively (45.9% vs. 49.8%, P = 0.455 and 14.7% vs. 14.0%, P = 0.894, respectively).

Outcomes

During the observation period, a total of three patients were hospitalized: one patient in the nirmatrelvir/ritonavir group and two patients in the molnupiravir group (P = 1.000). All hospitalizations were attributed to worsening symptoms and in patients aged 65 years and older. No deaths occurred.

Among patients prescribed nirmatrelvir/ritonavir, 79 (32.9%) experienced a total of 89 adverse events, whereas 48 (20.0%) patients in the molnupiravir group experienced 58 adverse events. This difference was found to be significant (P = 0.002) (**Table 2**). Regarding individuals aged 65 years and older, a significantly lower number of adverse events was reported for those receiving molnupiravir. However, regarding individuals under the age of 65 years, no significant difference was observed between the two antiviral agent groups. Overall, 95.8% of patients completed the treatment, whereas six (2.5%) and eight (3.3%) patients in the nirmatrelvir/ritonavir and molnupiravir groups, respectively, discontinued the medication because of adverse events. However, this difference was not significant (P = 0.786).

The most common adverse event in the nirmatrelvir/ritonavir group was dysgeusia, which occurred in 23.8% of patients, followed by nausea (n = 18, 7.5%), and dizziness (n = 5, 2.1%) (**Table 2**). In the molnupiravir group, nausea (n = 25, 10.4%) was the most frequently reported adverse event, followed by diarrhea (n = 8, 3.3%) and dizziness (n = 7, 2.9%). Four patients in the molnupiravir group developed skin rashes. All adverse events were of mild to moderate severity, with the symptoms improving after discontinuation of the medication.

Table 2. Prevalence of hospitalization, death, and adverse events during the oral antiviral regimen

Variables	Total (N = 480)	Nirmatrelvir/Ritonavir (n = 240)	Molnupiravir (n = 240)	P value
Hospitalization	3 (0.6)	1 (0.4)	2 (0.8)	1.000
Age, yr				
≥ 65 (n = 303)	3 (1.0)	1 (0.8)	2 (1.2)	1.000
< 65 (n = 177)	0 (0)	0 (0)	0 (0)	N/A
Death within 28 days	0 (0)	0 (0)	0 (0)	N/A
Any adverse events	127 (26.5)	79 (32.9)	48 (20.0)	0.002
Age, yr				
≥ 65 (n = 303)	68 (22.4)	43 (32.6)	25 (14.6)	< 0.001
< 65 (n = 177)	59 (33.3)	36 (33.3)	23 (33.3)	1.000
Dysgeusia	59 (12.3)	57 (23.8)	2 (0.8)	< 0.001
Nausea	43 (9.0)	18 (7.5)	25 (10.4)	0.338
Diarrhea	12 (2.5)	4 (1.7)	8 (3.3)	0.380
Dizziness	12 (2.5)	5 (2.1)	7 (2.9)	0.770
Skin rash	4 (0.8)	0 (0)	4 (1.7)	0.132
Severity of adverse events				0.175
Mild	466 (97.1)	236 (98.3)	230 (95.8)	
Moderate	14 (2.9)	4 (1.7)	10 (4.2)	
Severe	0 (0)	0 (0)	0 (0)	
Discontinuations	20 (4.2)	9 (3.8)	11 (4.6)	0.819
Discontinuation because of adverse events	14 (2.9)	6 (2.5)	8 (3.3)	0.786

Values are presented as number (%).
N/A = not applicable.

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Table 3. Multivariable logistic regression for adverse events

Variables	Overall		Nirmatrelvir/Ritonavir		Molnupiravir	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Oral antiviral agent type, nirmatrelvir/ritonavir	1.96 (1.27–3.03)	0.003				
Age, ≥ 65 yr	0.71 (0.46–1.11)	0.136	0.98 (0.55–1.76)	0.956	0.43 (0.22–0.86)	0.017
Sex, female	1.47 (0.96–2.26)	0.078	1.58 (0.89–2.80)	0.116	1.39 (0.69–2.78)	0.358
Appropriate vaccination	0.71 (0.44–1.14)	0.153	0.97 (0.53–1.75)	0.909	0.37 (0.15–0.91)	0.031
Comorbidity ≥ 2	1.12 (0.55–2.28)	0.745	1.24 (0.42–3.64)	0.701	1.04 (0.39–2.73)	0.940
Diabetes mellitus	0.98 (0.51–1.86)	0.941	0.86 (0.32–2.32)	0.773	1.07 (0.44–2.60)	0.889
Solid tumor	0.54 (0.18–1.61)	0.268	0.39 (0.09–1.61)	0.191	1.15 (0.20–6.68)	0.878
Cardiovascular disease	0.81 (0.33–2.01)	0.649	1.51 (0.44–5.15)	0.507	0.36 (0.07–1.90)	0.230
Chronic lung disease	2.60 (0.72–9.37)	0.143	2.83 (0.54–14.78)	0.219	4.03 (0.48–33.73)	0.199
Chronic kidney disease	2.66 (0.55–12.92)	0.224			4.44 (0.72–27.55)	0.109

CI = confidence interval, OR = odds ratio.

Factors associated with adverse reactions

Our study did not identify any risk factors associated with hospital admission. **Table 3** and **Supplementary Table 1** presents the factors associated with adverse events. Administration of nirmatrelvir/ritonavir (odds ratio [OR], 1.96; 95% confidence interval [CI], 1.27–3.03) was significantly correlated with a risk of adverse events. No significant risk factors for adverse events were found in the nirmatrelvir/ritonavir group. Conversely, within the molnupiravir group, age of 65 years and older (OR, 0.43; 95% CI, 0.22–0.86) and appropriate vaccination (OR, 0.37; 95% CI, 0.15–0.91) were significantly associated with a reduced risk of adverse events. Regarding patients under the age of 65 years, females had a higher risk of adverse events than males (OR, 2.08; 95% CI, 1.04–4.14) (**Supplementary Table 2**). For patients aged 65 years and older, only nirmatrelvir/ritonavir was significantly associated with adverse events (OR, 2.96; 95% CI, 1.67–5.23) (**Supplementary Table 3**).

DISCUSSION

During the ongoing COVID-19 pandemic, various attempts have been made to develop treatments using monoclonal antibodies and antiviral agents.[5,13,14] In the United States, nirmatrelvir/ritonavir and remdesivir are the preferred treatments, whereas molnupiravir is recommended as an alternative drug. This treatment approach is also recommended in Korea. To our knowledge, this is the first study to compare the effectiveness and safety of oral treatments for COVID-19 in Korea.

In this multicenter, prospective observational study, we found that the hospitalization rate did not significantly differ between outpatients treated with nirmatrelvir/ritonavir and those treated with molnupiravir for COVID-19. The hospitalization rate was low for both nirmatrelvir/ritonavir (0.4%) and molnupiravir (0.8%) groups, with no deaths being reported. Although adverse events occurred more frequently in the nirmatrelvir/ritonavir group than in the molnupiravir group, the rate of discontinuation because of drug-related adverse events was similar. Moreover, although hospitalization and mortality rates were low, approximately half of patients in both groups continued to report clinical symptoms even after 7 days of oral antiviral agent intake, with approximately 14% of them still experiencing clinical symptoms after 28 days.

Of note, vaccinated individuals were excluded from clinical trials regarding antiviral agents. In these trials, the therapeutic effects of the antiviral agents were observed to be 89% and 31% respectively.[4,5] However, in the real world, antiviral medication has been used in situations

where vaccination has already been initiated. Additionally, antiviral agents were clinically used during the Delta variant period and now during the omicron variant period, which may have resulted in different effectiveness compared with that in previous stages. Therefore, real-world data are crucial in assessing the impact of antiviral agents. Some notable findings on the effectiveness of nirmatrelvir/ritonavir and molnupiravir were published in 2022 when omicron variants were widespread globally. Most of these studies, which included vaccinated participants, reported that nirmatrelvir/ritonavir was effective in reducing hospitalization and mortality rates, despite the predominance of omicron and BA4/5 variants. However, the degree of effectiveness varied between studies.[15-22] Although nirmatrelvir/ritonavir is the preferred treatment, it should be replaced with molnupiravir in high-risk patients for whom the use of nirmatrelvir/ritonavir is restricted because of factors such as drug–drug interactions and renal insufficiency. In contrast to nirmatrelvir/ritonavir, few studies have evaluated the effectiveness of molnupiravir, and to this day their results have been inconsistent.[17,23-25]

Recent studies have directly compared the effectiveness of nirmatrelvir/ritonavir and molnupiravir in real-world settings. According to the results of a prospective study conducted by Tiseo et al.,[8] the rates of mortality and hospitalization were 0.8% and 1.8%, respectively, in high-risk outpatients who received nirmatrelvir/ritonavir and molnupiravir, showing no significant differences. In a retrospective observational study, the hospitalization and mortality rates were as low as 0.6–2.8% and 0.2–3.5% for nirmatrelvir/ritonavir and molnupiravir, respectively, with no significant difference between the two groups.[7,9,10] In our study, administration of nirmatrelvir/ritonavir and molnupiravir was associated with low hospitalization rates (0.4% and 0.8%, respectively) and no deaths, which was consistent with the findings of previous studies. Although we did not specifically analyze COVID-19 variants, BA5 and BN1 were predominant in Korea during the study period. We confirmed that oral COVID-19 treatments were associated with similarly low hospitalization rates during the BA5 and BN1 epidemics.

This study found that patients prescribed nirmatrelvir/ritonavir experienced an approximately 1.9 higher rate of adverse events than those prescribed molnupiravir. In a prospective study, the incidence of adverse events was significantly higher in patients treated with nirmatrelvir/ritonavir (49.2%) than those receiving molnupiravir (21.1%).[8] Similarly, Mazzitelli et al.[6] reported a significantly higher rate of adverse events in patients prescribed nirmatrelvir/ritonavir (19.1%) than those administered molnupiravir (6.9%). However, Mutoh et al.[7] did not observe a significant difference in the rate of adverse events between the two groups (5.3% for nirmatrelvir/ritonavir and 2.7% for molnupiravir). The most commonly reported symptoms in these studies included dysgeusia (9.0–41.9% in the nirmatrelvir/ritonavir group) and symptoms affecting the digestive system such as nausea, vomiting, and diarrhea (5.1–12.8% in the molnupiravir group).[6-8,10] Our study also found that dysgeusia was more frequent in patients administered nirmatrelvir/ritonavir than those receiving molnupiravir, whereas gastrointestinal symptoms were more prevalent in patients taking molnupiravir than those given nirmatrelvir/ritonavir. Although nirmatrelvir/ritonavir was associated with a higher rate of adverse events than that observed with molnupiravir, most of them were dysgeusia and were mild. In addition, the rate of drug discontinuation because of adverse events was similar in both groups. Our results indicated that nirmatrelvir/ritonavir can be safely used to treat COVID-19. Adverse events related to the administration of nirmatrelvir/ritonavir were only significantly observed in individuals aged 65 years and older. In our study, we found that appropriate vaccination reduced the incidence of adverse events in patients receiving molnupiravir. Therefore, molnupiravir may be the preferred treatment option for vaccinated older-aged patients who cannot take nirmatrelvir/ritonavir.

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This study had some limitations. First, we did not match or analyze confounding factors (e.g., patient characteristics) between the nirmatrelvir/ritonavir and molnupiravir groups. However, we found that molnupiravir was associated with more comorbidities but fewer adverse events than nirmatrelvir/ritonavir, while both groups had low hospitalization rates. Second, the lack of a control group prevented us from conclusively determining whether the adverse events were drug-related or caused by COVID-19 symptoms. Nonetheless, we observed an improvement in symptoms after drug discontinuation, suggesting a strong correlation with drug administration. Third, we did not investigate SARS-CoV-2 variant subtypes. However, we presume that most cases involved the BA5 and BN1 variants, which were predominant in Korea during the study period.

In conclusion, among high-risk patients with COVID-19, both hospitalization and death rates were low with either nirmatrelvir/ritonavir or molnupiravir treatments. Although nirmatrelvir/ritonavir had a higher incidence of adverse events than molnupiravir, none of the observed adverse events were serious, and the rate of drug discontinuation was similar for both treatments. Therefore, nirmatrelvir/ritonavir can be safely used to treat COVID-19, while molnupiravir could be considered as an alternative treatment option for high-risk groups.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
Indications for oral antiviral agents

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Supplementary Table 1
Univariable logistic regression for adverse events

Click here to view

Supplementary Table 2
Multivariable logistic regression for adverse events in patients aged under 65 years

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Supplementary Table 3
Multivariable logistic regression for adverse events in patients aged 65 years and older

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