ic Infection & Chemotherapy

Original Article

Check for updates

Nirmatrelvir/Ritonavir Prescription Rate and Outcomes in Coronavirus Disease 2019: A Single Center Study

Jin Ju Park (iD), **Jacob Lee** (iD), **Yu Bin Seo** (iD), and **Sun Hee Na** (iD)

Division of Infectious Diseases, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

🔓 OPEN ACCESS

Corresponding Author:
Jacob Lee, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Korea.
Tel: +82-2-829-5107
Fax: +82-2-6918-4222
Email: litjacob@chol.com

ORCID iDs
Jin Ju Park (iD)
https://orcid.org/0000-0002-5224-0837
Jacob Lee (iD)
https://orcid.org/0000-0002-7041-065X
Yu Bin Seo (iD)
https://orcid.org/0000-0001-5183-1996
Sun Hee Na (iD)
https://orcid.org/0000-0002-9605-7807

ABSTRACT

Background: Nirmatrelvir/ritonavir was Korea's first oral antiviral agent to treat coronavirus disease 2019 (COVID-19). We analyzed the nirmatrelvir/ritonavir prescription rate and treatment outcomes in treatment-eligible patients with COVID-19 receiving home-based care.
Materials and Methods: We retrospectively collected data of patients with COVID-19-eligible for nirmatrelvir/ritonavir treatment from January 14, 2022, to February 15, 2022. We analyzed the prescription rate of nirmatrelvir/ritonavir, the reasons for non-prescription, and patient outcomes.
Results: A total of 414 patients were included, of whom 44.2% were male, and the mean age was 64.6 (standard deviation [SD] = 8.5). Approximately 73.2% (n = 303) of patients were not prescribed nirmatrelvir/ritonavir. More than fourth-fifths of the patients refused nirmatrelvir/ritonavir treatment (n = 262, 86.5%). The mean symptom duration was significantly shorter in the prescription group (5.2 days [SD = 2.3] *vs.* 4.4 days [SD = 1.9], $P = 0.001$). A total of 6 (1.4%) patients were hospitalized, and none of the patients who received nirmatrelvir/ritonavir required admission. Among the patients prescribed nirmatrelvir/ritonavir (n = 111), 17 (15.3%) patients experienced side effects, and 5 (4.5%) patients discontinued nirmatrelvir/ritonavir due to side effects.
Conclusion: The nirmatrelvir/ritonavir prescription rate was low, with more than fourth-fifths of non-prescriptions being due to patient refusal. Symptom resolution was faster, and no life-threatening side effects were reported. Accurate information about drug safety must be provided to patients to make informed decisions regarding nirmatrelvir/ritonavir treatment.

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

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first discovered in Wuhan, China, in December 2019. Approximately 620 million cases of coronavirus disease 2019 (COVID-19) have been confirmed, and 6.5 million people have died of COVID-19 globally [1]. Various attempts have been made to end the COVID-19 pandemic. About 55.3% of the world's population has been vaccinated against COVID-19, and antiviral agents and monoclonal antibodies have also been studied to improve symptoms and prevent severe disease [2-8].

Nirmatrelvir/ritonavir (Paxlovid®, Pfizer, New York, NY, USA) was first approved by the US Food and Drug Administration as an oral antiviral agent for the treatment of COVID-19 [9]. Nirmatrelvir is a SARS-CoV-2 protease inhibitor, and ritonavir inhibits the metabolism of nirmatrelvir, causing it to remain in the body at a high concentration for a longer period [7]. A clinical trial by Pfizer, the developer of nirmatrelvir/ritonavir, reported that nirmatrelvir/ritonavir treatment reduced the risk of hospitalization or death from any cause by 89% compared to placebo [7]. Because it was administered orally and had proven effective in clinical trials, it was expected that the introduction of nirmatrelvir/ritonavir would significantly impact the COVID-19 pandemic. However, there were concerns that its prescription would be limited. Ritonavir is a potent inhibitor of cytochrome P450 CYP3A enzymes and interacts with CYP3A-dependent drugs [10]. In addition, nirmatrelvir/ritonavir must be taken within 5 days of symptom onset to be effective.

In Korea, nirmatrelvir/ritonavir was approved as an oral treatment agent for COVID-19 by the Korean Ministry of Food and Drug Safety on December 27, 2021 [11]. Treatment programs were introduced in home-based care patients and patients treated in community treatment centers on January 14, 2022 [12]. While the global COVID-19 pandemic goes on, for a continued drug introduction and use in the future, data on prescription, side effects, and effects of the drug would be important. This study aimed to investigate the prescription rate and outcomes of nirmatrelvir/ritonavir treatment among home-based care patients.

MATERIALS AND METHODS

1. Study design and patient selection
This retrospective study was performed at Kangnam Sacred Heart Hospital in patients with confirmed COVID-19 receiving home-based care from January 14, 2022, to February 15, 2022.

Patients qualified for nirmatrelvir/ritonavir treatment based on the following criteria: fulfillment of at least one point of criteria 1 and all points of criteria 2 [12, 13].

Criteria 1
From January 14 to 21, 2022: (1) patients 65 years of age or older; (2) immunocompromised patients [12].

From January 22 to February 6, 2022: patients aged 60 years or older; other indications remained the same.

From February 7, 2022, onwards: patients 50 years of age or older with comorbidities (diabetes mellitus, cardiovascular disorders such as hypertension, chronic renal disease, chronic lung disease including asthma, active cancer, overweight [body mass index ≥25 kg/m²], immunosuppression, sickle cell disease, or neurodevelopmental disorders); other indications remained the same.

Criteria 2
    1) Treatment could be initiated within 5 days of symptom onset.
    2) The patient did not require supplementary oxygen.

Nirmatrelvir/ritonavir was not prescribed in asymptomatic patients and contraindicated in patients using medications that interact with nirmatrelvir/ritonavir that could not be temporarily discontinued [14] and in those with severe renal or hepatic dysfunction.

Patients who satisfied at least one point of Criteria 1 were selected for the study.

2. Ethics statement
The study was approved by the Institutional Review Board (IRB) of Kangnam Sacred Heart Hospital (IRB No.2022-02-021). The requirement for informed consent was waived.

3. Nirmatrelvir/ritonavir treatment and home-based care monitoring
Kangnam Sacred Heart Hospital is a medical institution providing home-based care in agreement with Youngdeungpo-gu, Seoul, Korea. This institution receives and manages a list of patients with confirmed COVID-19 eligible for home-based care daily from a public health center. Home-based care nurses telephonically monitored the patient's condition twice daily (9 AM and 5 PM).

Patients were evaluated for nirmatrelvir/ritonavir treatment eligibility at the registered in home-based care. All indicated patients were informed about nirmatrelvir/ritonavir, and their intention to take the nirmatrelvir/ritonavir was confirmed in the first monitoring. With their consent, home-based care nurses provided the patient list to the doctor in charge. Nirmatrelvir/ritonavir was finally prescribed under the decision of the doctor in charge.

The prescription was sent to the public health center by fax, and nirmatrelvir/ritonavir was delivered to the patients' homes. Two pills of 150 mg nirmatrelvir and one pill of 100 mg of ritonavir should be taken together twice a day for 5 days. In the monitoring by home-based care nurses, the patients' COVID-19 symptoms, treatment adherence, and the development of side effects were collected.

4. Data collection and outcomes
We retrospectively reviewed the patient's electronic medical records and collected data on patient characteristics such as age, sex, comorbidities, COVID-19 positive test date, date of symptom onset, and current medication use.

We compared the characteristics and outcomes of patients who were prescribed nirmatrelvir/ritonavir with the characteristics of those who were not. The primary outcome of this study was the proportion of hospitalization. Moreover, the duration of the resolution of symptoms and the reasons for non-prescription were analyzed. When the patient did not complain of any special symptoms during monitoring, it was judged that the symptoms had resolved that day.

5. Statistical analysis
Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Statistical significance was assessed using the chi-square test and Fisher's exact test for categorical variables. Non-categorical variables were tested using the two-sided unpaired t-test or Mann–Whitney U test. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS (version 27.0, IBM, Chicago, IL, USA).

RESULTS

1. Characteristics of participants

A total of 625 patients qualified for the study, but 122 patients were asymptomatic from diagnosis to the conclusion of monitoring, 84 patients had more than 5 days of symptom onset, five patients were hospitalized on the day of first monitoring and excluded from the analysis; thus, 414 patients were analyzed in this study. Of these patients, 44.2% (n = 183) were men, and the mean age was 64.6 years (SD = 8.5) (**Table 1**). Patients with comorbidities numbered 244 (58.9%) and the most common comorbidity was hypertension (n = 135, 32.6%) followed by hyperlipidemia (n = 94, 22.7%), and diabetes mellitus (n = 63, 15.2%). A total of six (1.4%) patients were hospitalized, and 103 (24.9%) received medicine prescriptions.

Among the study participants, 303 (73.2%) patients were not, and 111 (26.8%) were prescribed nirmatrelvir/ritonavir (**Table 1**). There was no significant difference in sex, comorbidities, and asymptomatic at diagnosis between the prescription and non-prescription groups. Patients in the prescription group were older with significance (63.9 [SD = 9.2] *vs.* 66.2 [SD = 5.9], *P* = 0.003). The mean duration from symptoms to initial monitoring and mean duration of symptom resolution were significantly shorter in the prescription group (2.9 days [SD = 1.3] *vs.* 2.6 days [SD = 1.1], *P* = 0.030 and 5.2 days [SD = 2.3] *vs.* 4.4 days [SD = 1.9], *P* = 0.001). In the prescribed group, symptoms were resolved on a mean of 2.2 days after taking nitrmatrelvir/ritonavir, and in 90.1% of patients resolved within 4 days. None of the patients who received nirmatrelvir/ritonavir required admission to healthcare facilities because of clinical deterioration.

2. Outcomes and side effects

Of the patients prescribed nirmatrelvir/ritonavir, 17 (15.3%) experienced side effects, and 5 (4.5%) did not complete the treatment course owing to side effects (**Table 2**). Seven (6.3%) patients experienced nausea or heartburn, 5 (4.5%) diarrhea, 3 (2.7%) bitter taste, and 2 (1.8%) skin rash.

Table 1. Baseline characteristics of the study population (n = 414)

Characteristics	Total	Non-prescription (N = 303)	Prescription (N = 111)	*P*-value
	No (%)	No (%)	No (%)	
Sex				0.060
Male	183 (44.2)	125 (41.3)	58 (52.3)	
Female	231 (55.8)	178 (58.7)	53 (47.7)	
Age, years, mean (SD)	64.6 ± 8.5	63.9 ± 9.2	66.2 ± 5.9	0.003
Comorbidities	244 (58.9)	185 (61.1)	59 (53.2)	0.182
Hypertension	135 (32.6)	103 (34.0)	32 (28.8)	0.382
Hyperlipidemia	94 (22.7)	65 (21.5)	29 (26.1)	0.383
Diabetes mellitus	63 (15.2)	52 (17.2)	11 (9.9)	0.096
Thyroid disease	19 (4.6)	12 (4.0)	7 (6.3)	0.456
Others[a]	89 (21.5)	70 (13.1)	19 (17.1)	0.239
Asymptomatic at diagnosis	44 (10.6)	29 (9.6)	15 (13.5)	0.331
Mean duration from symptoms to monitoring[b], days (SD)	2.8 (1.2)	2.9 (1.3)	2.6 (1.1)	0.030
Mean duration for symptom resolution, days (SD)	5.0 (2.2)	5.2 (2.3)	4.4 (1.9)	0.001
Medicine prescription	103 (24.9)	82 (27.1)	21 (18.9)	0.117
Admission to healthcare facilities	6 (1.4)	6 (2.0)	0 (0.0)	0.303

[a]Angina, arrhythmia, psychiatric disorders, malignancy, stroke, epilepsy, chronic renal disease, asthma, human immunodeficiency virus infection, rheumatoid arthritis, ulcerative colitis, gout, Sjögren's disease, or ankylosing spondylitis.
[b]Analysis except asymptomatic at diagnosis (n = 370).
SD, standard deviation.

Table 2. Side effects of nirmatrelvir/ritonavir (n = 111)

Characteristics	No (%)
Nausea or heartburn	7 (6.3)
Diarrhea	5 (4.5)
Bitter taste	3 (2.7)
Skin rash	2 (1.8)
Total	17 (15.3)
Nirmatrelvir/ritonavir course completion	104 (93.7)

Table 3. Reasons for nirmatrelvir/ritonavir non-prescription in eligible patients (n = 303)

| Reasons	N (%)
Patient refusal	262 (86.5)
Use of interacting medicines	21 (6.9)
Hepatic/renal dysfunction	14 (4.6)
Admission to a healthcare facility before prescription	3 (1.0)
Use of an unknown medicine	3 (1.0)

3. Reasons for non-prescription of nirmatrelvir/ritonavir

The reasons for non-prescription are presented in **Table 3**. The most common cause was patient refusal (n = 262, 86.5%), followed by the use of interacting medicines (n = 21, 6.9%). The most commonly used interacting medicines were 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors such as rosuvastatin or atorvastatin (n = 20, 95.2%), followed by clopidogrel (n = 2, 1%), and phenobarbital (n = 1, 0.5%). Two patients were taking HMG-CoA inhibitors and clopidogrel.

DISCUSSION

As the COVID-19 pandemic continues, several drugs have been researched and developed to treat COVID-19 [4-8]. In Korea, previous studies examined the effectiveness of the treatment for Korean patients, and guidelines for the treatment have been published and updated [15-18]. Nirmatrelvir/ritonavir was the first oral antiviral agent approved by the US Food and Drug Administration and was the first oral antiviral agent used in Korea [8, 10]. In this study, we analyzed the initial cases of nirmatrelvir/ritonavir prescription and the resultant outcomes of COVID-19 patients receiving home-based care.

In the current study, only 26.8% of eligible patients received nirmatrelvir/ritonavir. The main reason for non-prescription was patients' refusal, accounting for 86.5%. The intention to take the nirmatrelvir/ritonavir was confirmed first in the at-home care monitoring for all patients who were indicated for nirmatrelvir/ritonavir. This proportion of refusal accurately reflected the patients' refusal intentions at the time of the initial introduction of nirmatrelvir/ritonavir. The reasons for patients' refusal were not investigated; however, some potential explanations could be discussed. First, patient concerns about drug safety and side effects may have driven this refusal, as nirmatrelvir/ritonavir was the first antiviral agent used to treat COVID-19 in Korea. Additionally, the Omicron variant, currently the most prevalent variant globally, is characterized by mild symptoms [19]. Consequently, patients were reluctant to risk trying a new medication. As this study was performed during the early stage of nirmatrelvir/ritonavir introduction, additional data should continuously be collected and analyzed to promote the safety and efficacy of the drug to patients.
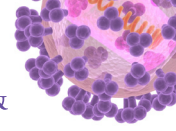
In 15.6% of cases, patients were ineligible for nirmatrelvir/ritonavir treatment because more than 5 days had elapsed since the onset of symptoms and were excluded from the analysis. Nirmatrelvir/ritonavir is more effective when administered in the early stages of symptoms, especially within 3 days of onset [7]. About 3.2 days elapsed from symptom onset to initial home-based monitoring. While patients were assigned to home-based care and contemplating taking their medication, the medication availability period might pass. In reality, it was shorter in nirmatrelvir/ritonavir prescription group. This suggests that the prescription could be smoothed out only when it was diagnosed as soon as symptoms occurred and information about it was provided. Rapid diagnosis and the dispensing system were critical to ensuring the efficacy of this drug.

In addition to treatment refusal, drug-drug interactions are one of the obstacles to prescribing nirmatrelvir/ritonavir. Ritonavir, a component of nirmatrelvir/ritonavir, potently inhibits CYP3A4. Many drugs, such as HMG-CoA reductase inhibitors and rifampin which CYP3A influences metabolism, showed drug-drug interaction with nirmatrelvir/ritonavir [10]. In this study, the most common drugs interacting with nirmatrelvir/ritonavir were HMG-CoA reductase inhibitors (statins), which are used to treat hyperlipidemia or other cardiovascular diseases. Depending on the type of statins, lovastatin, and simvastatin was contraindicated, and rosuvastatin and atorvastatin were recommended at the lowest possible dose [20]. Pravastatin and fluvastatin were recommended for use with nirmatrelvir/ritonavir among statins. Changing to a usable statin could be an option. National Institutes of Health recommended withholding these statins during nirmatrelvir/ritoniavir treatment and for at least 2 - 3 days after treatment completion [14]. Temporary discontinuation of these medicines and immediate contact with a medical institution with their abnormality was another option for allowing for nirmatrelvir/ritonavir treatment; however, this was challenging to implement due to the nature of home-based care. Changing medications during at-home care without face-to-face treatment or laboratory study was difficult. In addition, most of the patients were elderly and were interviewed telephonically; consequently, explaining which drugs needed to be discontinued and confirming their adherence presented significant difficulties. In our study, the proportion of non-prescription by interacting medicines was not as high as 6.9%, but among patients who refused prescriptions, those with dyslipidemia accounted for approximately 19.5%. Because the explanation for stopping concurrent medications after the prescription has been activated should not be a limitation, there should be a monitoring system in place that allows for a detailed explanation of the medications being taken. It is thought that further expanding monitoring through images would be helpful.

Studies by Pfizer and the Korea Disease Control and Prevention Agency reported a reduction in the risk of hospitalization and death by 89.1% and symptom improvement in 80.0% of patients taking nirmatrelvir/ritonavir, respectively [7, 21]. In the current study, symptoms were resolved within 2 days after taking nirmatrelvir/ritonavir in more than half patients. In addition, the duration of symptom resolution was significantly shorter in the prescription group. Although without statistical significance, none of the patients treated with nirmatrelvir/ritonavir required hospitalization compared to 2.0% of patients not prescribed. According to these results, the effect of preventing hospitalization was not clear, but it seems that there was an effect on the improvement of symptoms. At the beginning of the introduction of the drug, a small number of patients were targeted, and the severity was also low with the Omicron variant dominant, so a large-scale study on the drug's effect should be further conducted.

In a Korean survey, 69.1% of patients taking nirmatrelvir/ritonavir experienced a bitter taste, and 23.6% had diarrhea [17]. In the study by Pfizer, the incidence of adverse events was 22.6% [7]. In this study, only 15.3% of patients reported side effects of nirmatrelvir/ritonavir, with a third of them experiencing nausea or heartburn. This may be somewhat underestimated, as it mainly consisted of monitoring the patient's condition rather than the study to confirm the side effects. In 4.5% of cases, patients discontinued the drug owing to side effects, justifying close side effect monitoring in patients treated with nirmatrelvir/ritonavir.

This study had some limitations. First, it was a single-center study. Second, due to its retrospective nature and the fact that the patient's symptoms were checked through home-based care monitoring, the reporting of side effects and symptoms might be inaccurate. Third, as mentioned above, treatment refusal was high, but the reasons for refusal were not investigated. Further studies should analyze prescription data and their effectiveness over a longer time, and as nirmatrelvir/ritonavir starts to be administered nationwide, data should be collected from multiple centers.

In conclusion, we confirmed that among patients eligible for nirmatrelvir/ritonavir, the prescription rate was low and that more than fourth-fifths of non-prescriptions were due to patient refusal. However, symptom resolution was faster, and no life-threatening side effects were reported. Accurate information about drug safety must be provided to enable patients to make informed decisions regarding the choice of nirmatrelvir/ritonavir treatment.

REFERENCES

1. Johns Hopkins Coronavirus Resource Center. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available at: https://coronavirus.jhu.edu/map.html. Accessed 19 February 2022.

2. Our world in data. Coronavirus (COVID-19) vaccinations. Available at: https://ourworldindata.org/covid-vaccinations. Accessed 19 February 2022.

3. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.

4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J, Pedley A, Assaid C, Strizki J, Grobler JA, Shamsuddin HH, Tipping R, Wan H, Paschke A, Butterton JR, Johnson MG, De Anda C; MOVe-OUT Study Group. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2022;386:509-20.
   PUBMED | CROSSREF

5. Abbass S, Kamal E, Salama M, Salman T, Sabry A, Abdel-Razek W, Helmy S, Abdelgwad A, Sakr N, Elgazzar M, Einar M, Farouk M, Saif M, Shehab I, El-Hosieny E, Mansour M, Mahdi D, Tharwa ES, Salah M, Elrouby O, Waked I. Efficacy and safety of sofosbuvir plus daclatasvir or ravidasvir in patients with COVID-19: A randomized controlled trial. J Med Virol 2021;93:6750-9.
   PUBMED | CROSSREF

6. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383:1813-26.
   PUBMED | CROSSREF

7. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R, Rusnak JM; EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med 2022;386:1397-408.
   PUBMED | CROSSREF

8. Hong SI, Ryu BH, Hong KW, Bae IG, Cho OH. Real world experience with regdanvimab treatment of mild-to-moderate coronavirus disease-19 in a COVID-19 designated hospital of Korea. Infect Chemother 2022;54:114-24.
   PUBMED | **CROSSREF**

9. US Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19. Accessed 19 February 2022.

10. Hsu A, Granneman GR, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. Clin Pharmacokinet 1998;35:275-91.
    PUBMED | **CROSSREF**

11. Ministry of Food and Drug Safety. Emergency use approval of "Paxlovid", an oral COVID-19 treatment. Available at: https://www.mfds.go.kr/brd/m_99/view.do?seq=46032&srchFr=&srchTo=&srchWord=&srchTp=&itm_seq_1=0&itm_seq_2=0&multi_itm_seq=0&company_cd=&company_nm=&page=1. Accessed 19 February 2022.

12. Korea Centers for Disease Agency (KDCA). COVID-19 treatment guideline 4th edition. Available at: http://ncov.mohw.go.kr/shBoardView.do?brdId=2&brdGubun=24&ncvContSeq=5314. Accessed 19 February 2022.

13. Korea Disease Control and Prevention Agency (KDCA). COVID-19 treatment guideline 4. 2nd ed. Available at: https://www.kdca.go.kr/board/board.es?mid=a20507020000&bid=0019&act=view&list_no=7185. (in Korean). Accessed 19 February 2022.

14. National Institutes of Health (NIH). COVID-19 treatment guidelines. Ritonavir-boosted nirmatrelvir (Paxlovid). Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/. Accessed 15 February 2022.

15. Razzack AA, Hassan SA, Pasya SKR, Erasani G, Kumar S, Rocha-Castellanos DM, Lopez-Mendez A, Razzack SA. A meta-analysis of association between remdesivir and mortality among critically-Ill COVID-19 patients. Infect Chemother 2021;53:512-8.
    PUBMED | **CROSSREF**

16. Hong KS, Jang JG, Hur J, Lee JH, Kim HN, Lee W, Ahn JH. Early hydroxychloroquine administration for rapid severe acute respiratory syndrome coronavirus 2 eradication. Infect Chemother 2020;52:396-402.
    PUBMED | **CROSSREF**

17. Kim SB, Huh K, Heo JY, Joo EJ, Kim YJ, Choi WS, Kim YJ, Seo YB, Yoon YK, Ku NS, Jeong SJ, Kim SH, Peck KR, Yeom JS. Interim guidelines on antiviral therapy for COVID-19. Infect Chemother 2020;52:281-304.
    PUBMED | **CROSSREF**

18. Kim SB, Ryoo S, Huh K, Joo EJ, Kim YJ, Choi WS, Kim YJ, Yoon YK, Heo JY, Seo YB, Jeong SJ, Park DA, Yu SY, Lee HJ, Kim J, Jin Y, Park J, Peck KR, Choi M, Yeom JS; Korean Society of Infectious Diseases (KSID). Revised Korean Society of Infectious Diseases/National Evidence-based Healthcarea Collaborating Agency guidelines on the treatment of patients with COVID-19. Infect Chemother 2021;53:166-219.
    PUBMED | **CROSSREF**

19. Meo SA, Meo AS, Al-Jassir FF, Klonoff DC. Omicron SARS-CoV-2 new variant: global prevalence and biological and clinical characteristics. Eur Rev Med Pharmacol Sci 2021;25:8012-8.
    PUBMED

20. University of Liverpool. COVID-19 drug interaction. Available at: https://www.covid19-druginteractions.org/checker. Accessed 28 February 2022.

21. Korea Disease Control and Prevention Agency (KDCA). Investigation results of early administration of oral antiviral agents. Available at: https://www.kdca.go.kr/board/board.es?mid=a20501010000&bid=0015&list_no=718514&cg_code=&act=view&nPage=8. Accessed 15 February 2022.