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Nirmatrelvir plus ritonavir reduces COVID-19 hospitalization and prevents long COVID in adult outpatients

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Nirmatrelvir plus ritonavir received Emergency Use Authorization for treating mild to moderate COVID-19 in high-risk patients. Its efficacy against the Omicron variant of SARS-CoV-2 remains uncertain. This retrospective cohort study assessed the effect of nirmatrelvir–ritonavir in preventing severe disease progression and long COVID symptoms after acute COVID-19 in non-hospitalized adults. SALAMA medical records from Dubai's COVID-19 healthcare centers between May 22, 2022, and April 30, 2023, were used to identify 7290 eligible patients, 9.6% of whom received nirmatrelvir–ritonavir. Treatment was associated with a notable reduction in COVID-19-related hospitalizations (adjusted hazard ratio [HR] of 0.39; 95% CI, 0.18–0.85) by day 28 of symptom onset. Moreover, nirmatrelvir–ritonavir was associated with fewer long COVID symptoms (adjusted HR of 0.42; 95% CI, 0.19–0.95). This suggests the significant effectiveness of nirmatrelvir–ritonavir against the Omicron variant, reducing both severe and long-term COVID-19 symptoms.

Keywords Nirmatrelvir–ritonavir, Omicron variant, COVID-19, Long COVID, Hospitalization

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease 2019 (COVID-19) continue to threaten global health. Patients with underlying clinical conditions such as diabetes, cardiovascular disease, and obesity are at increased risk for severe COVID-19 and associated adverse outcomes[1]. These patients are more likely to progress to severe COVID-19, develop long-term COVID symptoms, and die from COVID-19[2,3].

Effective oral COVID-19 treatments are needed to prevent progression to severe disease. In December 2021, the Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for nirmatrelvir plus ritonavir to treat mild to moderate COVID-19 in adults and children aged 12 and older who are at increased risk of progressing to severe COVID-19[4]. Currently, the COVID-19 treatment guidelines provided by the National Institutes of Health (NIH) widely recommend that patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease be treated with either oral nirmatrelvir-ritonavir or intravenous remdesivir[5]. Although oral molnupiravir has been shown to reduce the risk of progression to severe COVID-19[6], it is listed as an alternative therapy to these options.

Nirmatrelvir is an oral antiviral agent that inhibits the 3-chymotrypsin–like cysteine protease enzyme (Mpro) of SARS-CoV-2, which is essential for the viral replication cycle[7]. Nirmatrelvir inhibits Mpro activity and virus replication across a broad spectrum of coronaviruses in vitro and in mouse infection models. Oral administration of nirmatrelvir resulted in significantly lower lung titers of SARS-CoV-2 compared to mice treated with a placebo[7]. Moreover, nirmatrelvir is metabolized mainly by CYP3A4; and therefore, its co-administration

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with ritonavir, which is a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor, increases the blood concentration of nirmatrelvir, enhancing its effectiveness against SARS-CoV-2[7,8].

COVID-19 has resulted in an increasing number of people recovering from SARS-CoV-2 infection. However, some individuals develop a prolonged and debilitating illness that persists for weeks or months. These 'Post-COVID conditions,' also known as 'Long COVID,' were defined by the Centers for Disease Control and Prevention (CDC) as symptoms that are present 4 or more weeks after acute SARS-CoV-2 infection[9]. Fatigue, breathlessness, chest pain, fever, palpitations, cognitive impairment, loss of smell, loss of taste, skin rash, and joint pain or swelling are among the reported symptoms[3,10]. The presence of long COVID symptoms is associated with COVID-19 severity, older age, and female gender[11,12]. Vaccination against SARS-CoV-2 has been shown to reduce the risk of long COVID by only about 15% in a study of more than 13 million people[13]. While this is the largest cohort to date used to study vaccines' effectiveness against the condition, it highlights the need for more robust preventive measures.

A small-scale study has shown a shorter viral shedding time in patients with COVID-19 who received nirmatrelvir-ritonavir early, within 5 days after the symptom onset, compared to those who received standard supportive care[14]. Although a few studies have shown the effectiveness of nirmatrelvir-ritonavir in preventing disease progression in high-risk patients[15,16], there is a lack of real-world clinical data during the Omicron variant period. Moreover, discrepancies exist regarding its effectiveness in lowering the risk of long COVID[17,18]. This report presents data on the effect of nirmatrelvir-ritonavir among symptomatic patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19 during the Omicron outbreak in Dubai, United Arab Emirates.

Methods

Study design

In this study, we analyzed administrative data from the SALAMA healthcare system in Dubai. SALAMA is the unified electronic medical record system used by Dubai Health Authority (DHA) hospitals and clinics, which work under a unified admissions and treatment system[19]. The study included data from patients who received oral antiviral nirmatrelvir-ritonavir (nirmatrelvir 300 mg plus ritonavir 100 mg orally twice daily for 5 days), and those who did not receive any antiviral treatment for COVID-19 between May 22, 2022, and April 30, 2023, at any of these DHA-affiliated hospitals and clinics. The retrieved data for each patient included demographics (age, gender, and ethnicity/race); dates of SARS-CoV-2 positive and negative reverse transcriptase–polymerase chain reaction (RT-PCR) results; COVID-19-related symptoms and oxygen saturation level (SpO2) at the time of diagnosis; date of prescription of nirmatrelvir-ritonavir; dates of the various doses of the COVID-19 vaccine; medical history at the patient level; details of the next visit, including the date, location (name of hospital or clinic), department (emergency department and/or family medicine), and the reported symptoms—pneumonia-related for emergency visits and long COVID symptoms for family medicine visits; survival status (alive or dead), and if deceased, the cause and date of death.

Ethical approval and consent to participation

This study received ethical approval from the Dubai Scientific Research Ethics Committee (DSREC) at Rashid Hospital (DSREC-12/2020_02). All patients' records were analyzed in a fully anonymized and de-identified manner, and researchers had no access to patients' personal information; hence, no written consent was required. This waiver of informed consent was approved by the Dubai Scientific Research Ethics Committee. Furthermore, all methods were performed in accordance with the relevant guidelines (Declaration of Helsinki and the Belmont Report) and regulations (DSREC rules).

Patients and treatment selection

The study included participants aged 18 years or older who tested positive for SARS-CoV-2 via RT-PCR and had mild to moderate COVID-19-related symptoms with SpO2 of $\geq$94% on room air, without requiring hospitalization[20]. Hospitalized patients with SpO2 levels below 94% or those needing supplemental oxygen were excluded.

The selection of patients for treatment with nirmatrelvir-ritonavir or no-treatment was based on the published national protocol for managing adult patients with COVID-19[21], and it also involved physician decision-making. The national protocol recommended administering nirmatrelvir-ritonavir within 5 days of symptom onset to high-risk individuals to prevent progression to severe COVID-19 and hospitalization[21]. This high-risk group included individuals aged $\geq$65 years, those with obesity ($\geq$25 kg/m^2), diabetes mellitus, cardiovascular disease or hypertension, chronic lung disease, individuals with immunocompromising conditions or on immunosuppressive treatment, chronic kidney disease, pregnant individuals, those with sickle cell anemia, neurodevelopmental disorders, and individuals dependent on medical-related technology such as tracheostomy[21]. Based on the protocol, patients with severe chronic kidney disease, defined as an eGFR of less than 30 mL/min, and those with severe liver disease were not recommended to receive nirmatrelvir-ritonavir[21]. Instead, they received other COVID-19 treatments, such as remdesivir or sotrovimab. These patients were also excluded from the no-treatment (control) group to avoid confounding factors. Moreover, all included patients did not receive molnupiravir, remdesivir, or sotrovimab, which were recommended for non-hospitalized patients at risk of COVID-19 progression.

Outcomes

In this study, the index date was defined as the date of a positive SARS-CoV-2 RT-PCR test result, which indicated an acute COVID-19 diagnosis and prescription of nirmatrelvir-ritonavir. The primary outcome assessed was the risk of COVID-19-related hospitalization up to day 28, with both the nirmatrelvir-ritonavir treated group and

the no-treatment group followed for 28 days post-acute COVID-19 diagnosis (Fig. 1). During the emergency department visit, patients were evaluated for COVID-19 pneumonia as the primary diagnosis, and hospitalization lasting more than 24 h was considered. The secondary outcome was evaluated as a patient visit to the family medicine department due to the symptom(s) of long COVID, defined as continuous or new symptom(s) present 28 days or more following acute COVID-19 infection[9,22,23]. The physician notes were evaluated for the presence of these symptoms (as shown in Fig. 2A and B) reported by the patients. Both the nirmatrelvir-ritonavir treated group and the no-treatment group were followed for 90 days post-acute COVID-19 diagnosis for this secondary outcome.

Statistical analysis

For descriptive analysis, means and standard deviations or medians and interquartile ranges were used for continuous data, as appropriate. Chi-square tests were used to compare percentages across treatment groups for categorical variables.

To determine the risk of COVID-19-related hospitalizations and the risk of developing long COVID symptoms, we developed Cox proportional hazards models adjusted for patients' demographics (age, gender, ethnicity/race), pre-existing conditions (diabetes mellitus, overweight, cardiovascular disease, hypertension, autoimmune disorder, malignancy), and vaccination status. Kaplan-Meier survival curves were constructed to show cumulative survival. We tested all variables for multicollinearity to avoid strong correlations. Standard errors and variance inflation factors were evaluated for collinearity.

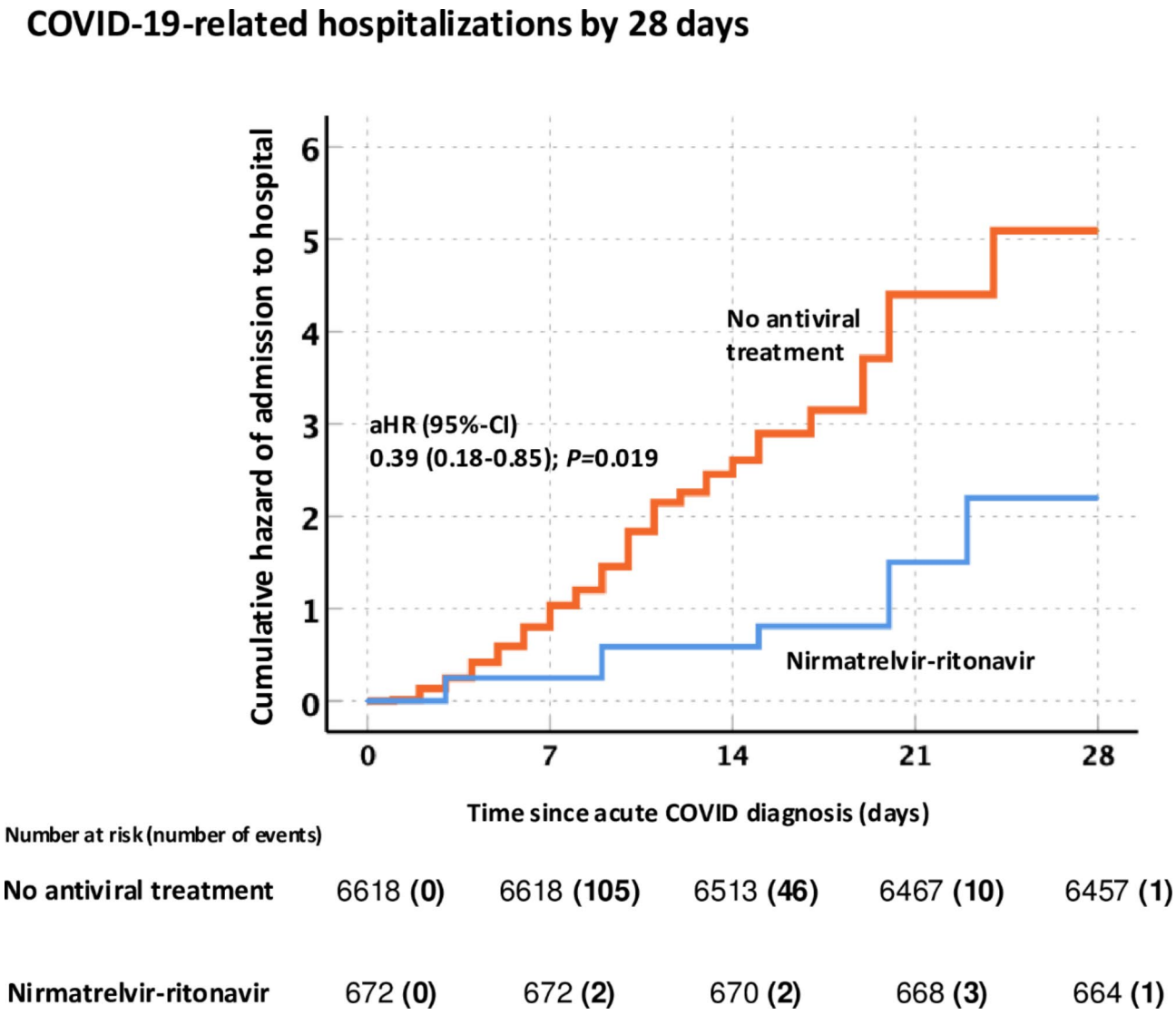

Fig. 1. The effect of nirmatrelvir-ritonavir on COVID-19-related hospitalization through 28 days of treatment initiation. Kaplan-Meier plot comparing individuals not treated and those treated with nirmatrelvir-ritonavir. A cumulative hazard value of 5 for no antiviral treatment indicates that the risk of hospital admission over 28 days is five times the baseline risk, while a value of 2 for nirmatrelvir-ritonavir indicates a risk that is twice the baseline over the same period. Abbreviations: HR, Hazard ratio.

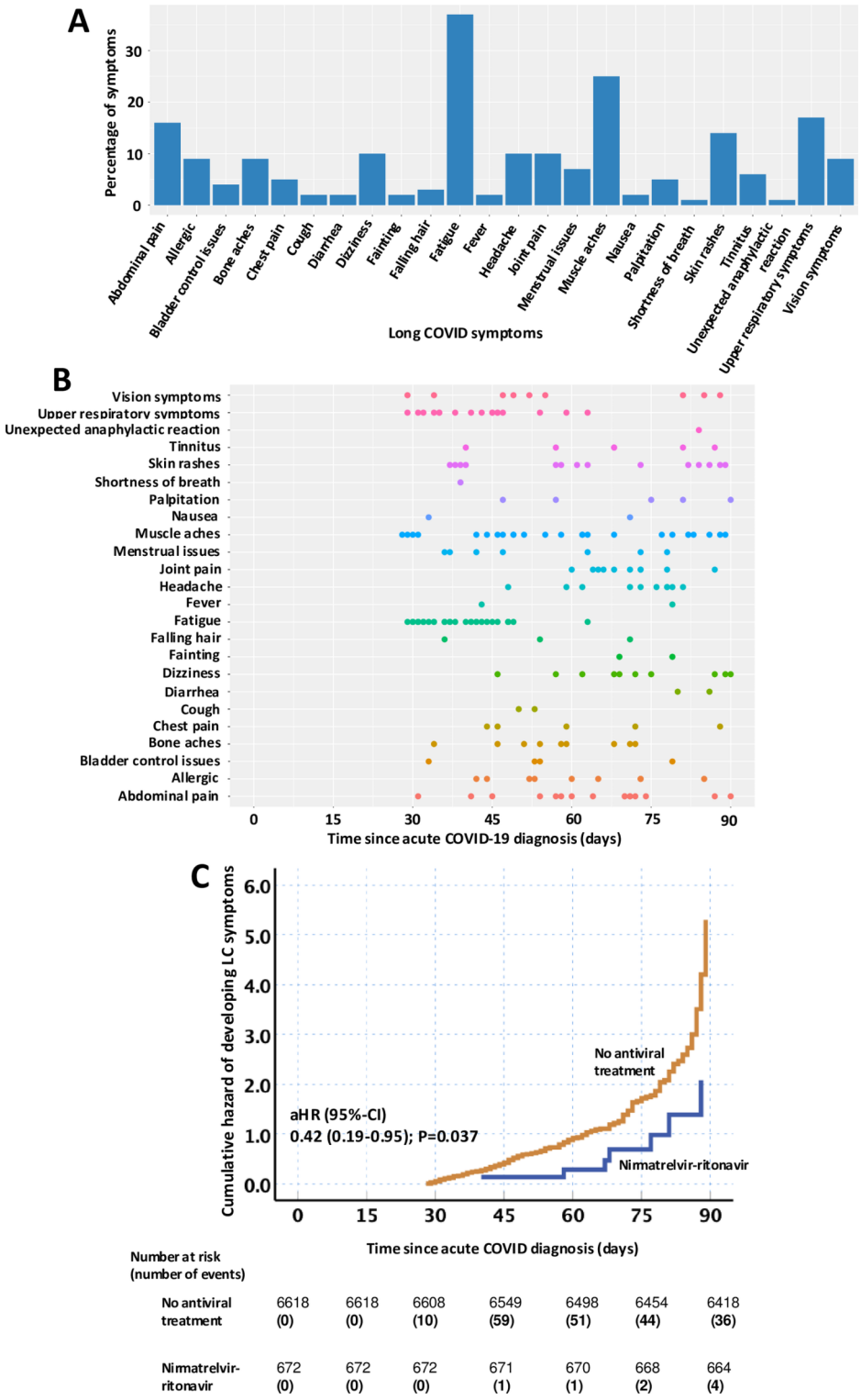

Fig. 2. The effect of nirmatrelvir-ritonavir on long COVID symptoms reported within 90 days of treatment initiation. (**A**) Frequency of each reported symptom (**B**) Time of each reported symptom within 90 days from the acute COVID infection. (**C**) Kaplan-Meier plot comparing individuals not treated and those treated with nirmatrelvir-ritonavir. A cumulative hazard value of 5 for no antiviral treatment indicates that the risk of developing long COVID over 90 days is five times the baseline risk, while a value of 2 for nirmatrelvir-ritonavir indicates a risk that is twice the baseline over the same period. Abbreviations: HR, Hazard ratio.

We analyzed the data using SPSS software (version 26.0), R software (version 3.6.1), and PRISM software (version 8).

Results

Patient characteristics

Among the 7290 non-hospitalized adults with COVID-19 in the SALAMA system who met the study criteria, 672 received nirmatrelvir-ritonavir, while 6618 received no antiviral treatment. Table 1 presents the baseline characteristics of patients at treatment initiation. As shown, patients in the nirmatrelvir-ritonavir group were relatively older than those in the no-treatment group (54 years in the nirmatrelvir-ritonavir group versus 37 years in the no-treatment group; $P<0.001$). In both groups, approximately half of the patients were male (48% in the nirmatrelvir-ritonavir group and 45% in the no-treatment group; $P=0.102$), and two-thirds were Caucasian (81% in the nirmatrelvir-ritonavir group and 78% in the no-treatment group, $P=0.090$). Approximately half of the patients in both groups had received two doses of the COVID-19 mRNA vaccine (45% in the nirmatrelvir-ritonavir group and 48% in the no-treatment group; $P=0.187$) (Table 1).

Furthermore, among all the risk factors for COVID-19 progression included in the guidelines[21], the most common were being 65 years or older, diabetes, overweight status, cardiovascular disease, hypertension, asthma, and immunocompromised conditions. These factors were more prevalent in the nirmatrelvir-ritonavir group than in the no-treatment group. In the nirmatrelvir-ritonavir group, 32% of patients were aged 65 and older compared to 12% in the no-treatment group ($P<0.001$). Diabetes mellitus was present in 28% of patients in the nirmatrelvir-ritonavir group versus 10% in the no-treatment group ($P<0.001$). Additionally, 16% of patients in the nirmatrelvir-ritonavir group were overweight compared to 8% in the no-treatment group ($P<0.001$). Cardiovascular disease was present in 11% of patients in the nirmatrelvir-ritonavir group versus 4% in the no-treatment group ($P<0.001$). Hypertension was observed in 29% of patients in the nirmatrelvir-ritonavir group compared to 13% in the no-treatment group ($P<0.001$). Asthma was more prevalent in the nirmatrelvir-ritonavir group, affecting 4% compared to 2% in the no-treatment group ($P=0.008$). Immunocompromised conditions, such as autoimmune disorders and malignancies, were more prevalent in the nirmatrelvir-ritonavir group compared to the no-treatment group ($P=0.004$) (Table 1).

Nirmatrelvir-ritonavir reduces COVID-19 hospitalization within 28 days after acute COVID-19

In the 7290 patients treated with nirmatrelvir-ritonavir or not treated with antiviral medication, 170 (2.3%) COVID-19-related hospitalizations lasting > 24 h were observed over a 28-day period following diagnosis of COVID-19. These included 8 (1.1%) in the nirmatrelvir-ritonavir group and 162 (2.4%) in the no-treatment group. Cox regression analysis showed that, after adjusting for patient demographics, pre-existing conditions, and vaccination status, treatment with nirmatrelvir-ritonavir was associated with a lower risk of 28-day COVID-19-related hospitalization compared to no-treatment (adjusted HR for nirmatrelvir-ritonavir, 0.39, 95% CI: 0.18–0.85, P=0.019 (Fig. 1).

Characteristics	Nirmatrelvir-ritonavir ($n=672$)	No antiviral treatment ($n=6618$)	P-Value
Age, median (range)- yr	54 (42–68)	37 (28–51)	< 0.001
Male sex, no (%)	324 (48)	2973 (45)	0.102
[a]White, no (%)	546 (81)	5191 (78)	0.090
[b]Vaccination status, no. (%)	306 (45)	3190 (48)	0.187
Risk factors for COVID-19 progression—no. (%)			
Age ≥ 65 yr	215 (32)	774 (12)	< 0.001
Diabetes Mellitus	186 (28)	682 (10)	< 0.001
Overweight (BMI ≥ 25 kg/m^2)	108 (16)	533 (8)	< 0.001
Cardiovascular diseases	75 (11)	259 (4)	< 0.001
Hypertension	192 (29)	836 (13)	< 0.001
[c]Chronic kidney disease	23 (3)	156 (2)	0.089
Asthma	27 (4)	155 (2)	0.008
[d]Autoimmune disorder	18 (3)	79 (1)	0.004
[e]Malignancy	8 (1)	11 (0.2)	< 0.001
Oxygen saturation, SpO2, median (range)	99 (97–99)	99 (97–100)	0.187

Table 1. Baseline characteristics of patients receiving nirmatrelvir-ritonavir, or no antiviral treatment for COVID-19. [a]White ethnicity or Caucasian race. [b]Receiver of 2 doses of mRNA vaccines. [c]Chronic kidney disease is defined as an eGFR of 30 to 60 mL/min. [d]Autoimmune disorders include any of Addison's disease, celiac disease, dermatomyositis, Hashimoto thyroiditis, inflammatory bowel disease, Multiple sclerosis, reactive arthritis, rheumatoid arthritis, or systemic lupus erythematosus. [e]Malignancy refers to any type of cancer receiving chemotherapy and/or radiation treatment. Abbreviations: BMI, Body mass index.

Nirmatrelvir-Ritonavir reduces long COVID symptoms

Throughout the 90-day follow-up period, out of 7290 COVID-19 cases, 208 (2.8%) patients experienced long COVID symptoms that warranted a visit to the family medicine department. Of these, 8 patients (1.1%) were in the nirmatrelvir-ritonavir group compared to 200 patients (3%) in the no-treatment group ($P=0.015$). Fatigue (17.8%), muscle pain (12%), and upper respiratory symptoms (8.2%) were the most commonly reported symptoms (Fig. 2A). The distribution of long COVID symptoms remained relatively consistent for most symptoms during this period (Fig. 2B). Adjusted Cox regression analysis revealed that treatment with nirmatrelvir-ritonavir was associated with a reduced risk of developing long COVID symptoms during the 90-day follow-up period (adjusted HR for nirmatrelvir-ritonavir, 0.42; 95% CI, 0.19–0.95, $P=0.037$) (Fig. 2C).

Discussion

The results of this population-based study indicate that the early administration of nirmatrelvir-ritonavir to high-risk patients was effective in reducing COVID–19–related hospitalization by day 28 from the start of treatment. Given that the most common variant during our study was Omicron (BA.4/5), this suggests the efficacy of the treatment against these variants of SARS-CoV-2. Other population-based studies have reported similar benefits from nirmatrelvir-ritonavir during Omicron variant outbreaks[24,25]. Since nirmatrelvir targets the highly conserved viral protein Mpro active site[7], it is likely to maintain efficacy against emerging Omicron subvariants, a potential limitation of neutralizing monoclonal antibody therapy. In vitro testing has also shown that Omicron subvariants remain relatively susceptible to nirmatrelvir[26].

Another noteworthy finding of our study is that treatment with nirmatrelvir-ritonavir during the acute phase of COVID-19 was associated with a decreased risk of developing long COVID in high-risk groups. Previous studies with different sample sizes and designs have confirmed that nirmatrelvir-ritonavir reduces long COVID symptoms compared to the no-treatment group[17,18]. This effect is likely due to the relationship between viral persistence and long COVID symptoms[27], as treatment may reduce viral load and, subsequently, long COVID symptoms. Our previous population-based observations suggested that the prevalence of long COVID is reduced with other antiviral treatments, such as favipiravir, and more significantly with the monoclonal antibody sotrovimab, compared to no antiviral treatment[22]. Clinically, it is significant that oral nirmatrelvir-ritonavir during the acute phase not only reduces the risk of hospitalization but also decreases long COVID symptoms. However, further research is needed to understand the molecular mechanisms behind this effect.

The strength of this study lies in its inclusion of all adult patients with a positive PCR test for COVID-19 during the study period, regardless of whether they received nirmatrelvir-ritonavir or not, allowing the findings to be more generalizable and representative of real-world clinical data. This regional data can inform decision-makers about the overall effectiveness of nirmatrelvir-ritonavir in reducing the burden of disease in both the acute and post-acute phases of COVID-19. However, the study also has several limitations. First, we were unable to determine the safety of nirmatrelvir-ritonavir in the treated group due to the retrospective nature of the study. Ritonavir may increase the blood concentration of certain concomitant medications; however, drug interactions with low-dose ritonavir (100 mg) given over a short duration of 5 days for the treatment of COVID-19 are less likely to be of clinical consequence than the long-term use of ritonavir for patients with human immunodeficiency virus. Second, our study was not a randomized controlled trial. Therefore, we cannot completely rule out the possible impact of bias due to unmeasured patient factors or other residual confounding that may affect the study outcomes. However, the adequate number of events in the study allowed us to adjust for many potential confounders in the developed models. Third, we might have missed the COVID-19-related hospitalizations or long COVID episodes of those patients who visited hospitals outside the coverage of the Government of Dubai and the SALAMA system, although the chances are low as these hospitals are the only places providing free COVID-19-related treatment to these patients in the city of Dubai. Finally, since long COVID symptoms were assessed based on patient-reported symptoms during the visit to the family medicine department and the physician's report, there may be potential for reporting bias in symptoms by both the patient and the physician. Additionally, we may have also missed patients with long COVID because some may not have sought medical attention due to their lack of knowledge or understanding of the condition or because their symptoms were mild and did not require medical care.

In conclusion, administering nirmatrelvir-ritonavir to COVID-19 reduced the risk of COVID-19-related hospitalization and the occurrence of long COVID symptoms after acute COVID-19 when compared to the no-treatment group, especially for high-risk patients.

Data availability

All data analyzed during this study are deposited in Supplementary File.

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Author contributions

F.S.S.A., H.A.H.A., N.S.S.A., A.A.S.H., S.A.M. and R.H., wrote the manuscript; F.S.S.A., H.A.H.A., N.S.S.A., and R.H., designed the research; F.S.S.A., H.A.H.A., A.A.S.H., and N.S.S.A., performed the research; F.S.S.A. analyzed the data; R.H., contributed new reagents/analytical tools.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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