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Nirmatrelvir-ritonavir efficacy and safety in high-risk COVID-19 patients: a review of recent retrospective cohort studies – nephrology point of view

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ABSTRACT

The COVID-19 pandemic has prompted researchers to look for efficient treatments to lower high-risk patients' probabilities of hospitalization, rapid disease progression, and death. Nirmatrelvir-ritonavir (Paxlovid) is a promising treatment option that has been evaluated in several recent retrospective cohort studies. In this article, we review four such studies conducted in China and the USA between 2022 and 2023. The studies, which included large groups of COVID-19 patients, found that Paxlovid treatment was linked to a significant drop in the risk of hospitalization, severe disease progression, and death in high-risk patients. This was true even for patients who had been immune to the disease before from an infection or vaccination. However, more research is needed to validate these results and evaluate the long-term efficacy and safety of this medication. In addition to highlighting the need for larger studies to evaluate both the effectiveness and safety of this treatment in patients with a variety of populations, our review sheds light on the present understanding of Paxlovid and its application for high-risk COVID-19 patients.

Review

Implication for health policy/practice/research/medical education:
A review of recent retrospective cohort studies found that nirmatrelvir-ritonavir (Paxlovid) has a big impact on lowering the chances of hospitalization, severe disease progression, and death in high-risk COVID-19 patients, even those who had immunity before. To confirm these results and evaluate Paxlovid's long-term effectiveness and safety in a variety of patient population demographics, more studies must be conducted.

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Introduction

The outbreak of the COVID-19 pandemic was one of humanity's most catastrophic incidents of the twenty-first century so far. By resulting in many different kinds of injuries, this SARS-CoV-2 disease was one of the most destructive to people's lives and property throughout the world. The SARS-CoV-2 pandemic was publicly stated by the World Health Organization (WHO) in March 2020. The rapid spread, absence of appropriate treatments, severity, and unpredictability of COVID-19 caused an enormous challenge to medical staff, supervisors, and healthcare systems. 765 903 278 confirmed COVID-19 cases, including 6 927 378 mortalities, as of May 14, 2023 (1). The majority of people diagnosed with coronavirus disease 2019, which is brought on by SARS-CoV-2, usually recover from acute infection with minimal medical support. However, the progression of clinical symptoms into a serious illness that necessitates hospitalization can have a major impact on the patient's health (including mortality) and the healthcare system. Thus, lowering hospitalization and mortality is one of the pandemic's most critical objectives (2-4).

Treatment options for SARS-CoV-2 infection include some antivirals, monoclonal antibodies, and immunomodulatory medications. Patients should be observed for hypersensitivity reactions (including anaphylaxis) for at least an hour after receiving monoclonal antibody therapy, which can be given as a

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subcutaneous injection or intravenous infusion. However, there are restrictions on the use of monoclonal antibodies in outpatients with COVID-19, and you must consider their limited supply outside of the manufacturing country as well as the fact that they are less effective against more recent strains of SARS-CoV-2. One of these limitations is that monoclonal antibodies might not be able to respond as well to new strains of SARS-CoV-2 that have changed spike proteins (5–9). Remdesivir is the only antiviral medication that the U.S. Food and Drug Administration has approved for use in both adult and pediatric COVID-19 patients who require hospitalization. Remdesivir must be given in a healthcare setting with ongoing monitoring as well as through infusion or injection (10).

Paxlovid emergency use authorization

The US FDA recently granted Emergency Use Authorization (EUA) for two oral antiviral medications for adult outpatients with mild to moderate COVID-19. Pfizer's nirmatrelvir plus ritonavir (Paxlovid in the US) and Ridgeback/Merck's molnupiravir (Lagevrio in the US) received EUA on December 22 and 23, 2021, respectively (11).

Paxlovid's EUA was for the treatment of children and adults (over twelve years old and more than 40 kg) who had a mild to moderate COVID-19 infection and were at a high risk of the disease advancing to a severe form. An interim analysis of the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial led to the decision to grant the EUA. The trial included adults who were not hospitalized, had been diagnosed with SARS-CoV-2, had symptoms, and had at least one risk factor for progression to severe disease. The interim analysis's findings revealed a decrease in the probability of hospitalization caused by COVID-19 and an 88% reduction in mortality in the group receiving Paxlovid compared to the control group receiving a placebo during the 28-day follow-up (12-14).

Paxlovid pharmacokinetics

Patients with mild to moderate disease receive Paxlovid for five days straight. It contains nirmatrelvir, a primary SARS-CoV-2 protease inhibitor that specifically targets the 3C-like protease of the virus. Nirmatrelvir is also a substrate and potential inhibitor of the P-glycoprotein and CYP3A4 enzymes. In addition, nirmatrelvir metabolism is slowed down, and its serum levels are raised by using ritonavir as a CYP3A4 inhibitor. Besides that, ritonavir activates glucuronosyltransferase, CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2B6, and other enzymes (15,16).

Paxlovid drug interactions

Nirmatrelvir must be administered with ritonavir because it boosts nirmatrelvir levels and is necessary for its use. Co-administration of nirmatrelvir-ritonavir and drugs with a high dependence on the enzymes mentioned above can cause significant and life-threatening changes in the concentration of those drugs, hence it is contraindicated. For example, the level of warfarin may increase or decrease at a mild to moderate level when a patient takes nirmatrelvir-ritonavir, which necessitates monitoring patients during treatment (16,17).

Paxlovid side effects

In a clinical trial, adverse reactions occurred more often in the group treated with nirmatrelvir-ritonavir than in the control group within 34 days from the start of the study. Common side effects were dysgeusia (6% in the group receiving the medication and less than 1% in the control group), diarrhea (3% in the group receiving the medication and 2% in the control group), hypertension (1% in the group receiving the medication and less than 1% in the control group), and myalgia (1% in the group receiving the medication and less than 1% in the control group) (16,18).

Paxlovid dosage

Nirmatrelvir-ritonavir, which comes in tablets of 150 mg nirmatrelvir and 100 mg ritonavir packaged together, is only to be taken orally. The recommended dosage is 100 mg of ritonavir and 300 mg of nirmatrelvir every 12 hours with or without food for five days. Nirmatrelvir dosage should be decreased to 150 mg every 12 hours in moderate renal failure (glomerular filtration rate greater than 30 and less than 60), but ritonavir dosage does not need to be altered. This is true, and although mild renal failure (glomerular filtration rate greater than 60 mL/min and less than 90 mL/min) does not require dose adjustment, Nirmatrelvir-ritonavir should not be used in patients with severe renal failure (glomerular filtration rate less than 30 mL/min) due to a lack of information on the appropriate dosage. In patients with mild to moderate liver failure (Child-Pugh Classes A to B), nirmatrelvir-ritonavir does not require dosage adjustments, but it is not suggested to use this medication in patients with severe liver failure (Child-Pugh Class C) due to inadequate knowledge about its pharmacokinetics and safety (16).

Method of study

For this study, the information sources of PubMed, Google Scholar, Scopus, Science Direct, Elsevier, and a detailed search strategy by specifying keywords related to the subject through MeSH terms were conducted to find articles. Keywords were; SARS-CoV-2, COVID-19, Paxlovid, remdesivir, nirmatrelvir, ritonavir and glomerular filtration rate. Four articles published between May 2022 and May 2023 were reviewed, each with an adequate number of total patients and patients treated with nirmatrelvir-ritonavir, as follows.

Literature review

A retrospective cohort study in China between February 22 and March 31, 2022, investigated the effect of molnupiravir and nirmatrelvir-ritonavir on patient mortality, the probability of hospitalization in outpatients, and the probability of re-hospitalization in hospitalized patients within 28 days of treatment. Mild to moderate COVID-19 patients over the age of 60 or younger with at least one underlying chronic disease were included in the study, and both medications were administered for a total of five days. Around 13.4% of outpatients and 1.3% of hospitalized patients received nirmatrelvir-ritonavir. In this study, patient characteristics were modified using Inverse Probability of Treatment Weighting (IPTW). According to the IPTW-adjusted Cox model, nirmatrelvir-ritonavir therapy is significantly linked to a decrease in COVID-19-related mortality (HR = 0.10; 95% CI: 0.05-0.21, $P < 0.0001$). Nirmatrelvir-ritonavir therapy significantly lowered the probability of re-hospitalization within 28 days of starting therapy in hospitalized patients (OR = 0.47; 95% CI: 0.24-0.93, $P = 0.030$) and was linked to a decreased risk of unexpected hospitalization in outpatients (OR = 0.37; 95% CI: 0.23-0.60, $P<0.0001$) (19).

Between January 1 and May 15, 2022, 78 474 COVID-19 patients participated in a retrospective cohort study at Brigham, of which 31,460 were 50 years of age or older and eligible for the study. To ensure the criteria were equal, 1138 of these patients had their initial diagnoses at the time of hospitalization or death. The remaining 30 322 patients had an outpatient diagnosis and were eligible for treatment with nirmatrelvir and ritonavir. The study evaluated factors such as age, patient medical conditions, vaccination status and the last vaccine received, comorbidity, race types, socio-economic status, and body mass index. Patients who had active cancer, received immunosuppressive medications while immunocompromised, had solid organ or stem cell transplants, or were HIV-positive were all taken into consideration. The exclusion criteria of the study were patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min, patients taking medications for which co-administration of nirmatrelvir plus ritonavir is not suggested, and patients who have received other COVID-19 treatments that have been approved, such as anti-SARS CoV-2 monoclonal antibodies, molnupiravir, and ambulatory remdesivir. The main objective of the study was to assess whether or not nirmatrelvir and ritonavir reduced the risk of hospitalization in the 14 days after an outpatient diagnosis of COVID-19. As a secondary outcome evaluation, deaths that were recorded within 28 days of the diagnosis of COVID-19 were included. Within the first five days following the start of symptoms, patients were given nirmatrelvir plus ritonavir. It was given to 6036 patients, and older patients who had more comorbid conditions and were given all recommended vaccinations were more likely to receive it. In this study, hospitalizations occurred in 40 patients (0.66%) who got nirmatrelvir plus ritonavir and 232 patients (0.96%) who did not get nirmatrelvir plus ritonavir within 14 days of the diagnosis of COVID-19 infection. Age, socioeconomic vulnerability, and comorbidities were equivalent variables. Among the 30 322 study participants who were diagnosed as outpatients, 39 deaths were noted within 28 days following the diagnosis of COVID-19. Patients who did not get nirmatrelvir and ritonavir were the only ones who died. Thirteen people passed away after getting a COVID-19 hospital diagnosis, and 28 (74%) of those deaths were vaccine recipients (20).

In a retrospective cohort study conducted by Shah et al in the United States, 1713 120 participants aged 18 and above with a COVID-19 diagnosis from April 1 to August 31, 2022, were included. Finally, 699 848 people (40.9%) were susceptible to the COVID-19 infection and at risk of developing severe illness. Among these eligible individuals, 198 927 people (4.28%) received Paxlovid within the first 5 days of diagnosis, while 500 921 people (6.71%) did not receive it. Eligible people in this study included those who had a positive test for SARS-CoV-2, mild to moderate symptoms for COVID-19, only 5 days have passed since the onset of symptoms, age more than 18 years, one or more risk factors for progression to severe disease, do not have a history of hypersensitivity reactions, and do not use drugs that interfere with Paxlovid. Pregnant women, people who have taken drugs with contraindications to Paxlovid in the last 6 months, people under 50 years old without underlying disease, people who were hospitalized on the day of diagnosis, people who had severe kidney and liver failure, and people who received other drugs for the treatment of COVID-19 were excluded. Age, gender, race, social class, geographical location, the type of patient meeting, underlying disease conditions, immune system deficiencies, prior infections, obesity, smoking, diabetes, and vaccination status were assessed in this study. The link between Paxlovid administration and hospitalization has been investigated using the Cox proportional hazards model. Hospitalization for COVID-19 within 30 days of diagnosis was the study's major objective, while secondary outcomes were hospitalization for other conditions as well as hospitalization due to acute respiratory disease. About 68.8% of the COVID-19 patients who were eligible for Paxlovid had received two or more doses of the COVID-19 mRNA vaccine, whereas 15% had prior infection evidence. The prevalence of underlying diseases was similar among Paxlovid recipients and non-recipients, and 92.4% of subjects had at least one underlying disease. People with immunodeficiency accounted for 9.4% (64 911) of the population, and 5229 (0.75%) were hospitalized after 30 days from the diagnosis of the disease, of which 3311 (63.3%) occurred among people over and equal to 65 years of age. Among the 198 927 people who received Paxlovid, 930 (0.47%) were

hospitalized, while among those who did not receive the medicine, this statistic was 4299 (0.86%). Amongst hospitalized subjects, 930 (17.8%) received Paxlovid for 5 days, and 211 deaths were reported among those hospitalized. The death rate among people who received the drug was 0.01%, while it was 0.04% among people who did not receive the drug. In individuals with mild to moderate COVID-19 symptoms, Paxlovid decreases the probability of hospitalization by 51%. According to this study, using Paxlovid to treat patients who already have protection from a prior illness or immunization may also decrease the risk of hospitalization (21).

The drug nirmatrelvir-ritonavir (Paxlovid) was tested in a retrospective cohort study in another country using the database of that country's main healthcare provider to see how well it worked at lowering the severe form of COVID-19 and patients' deaths from this illness. 180,351 individuals who were over 18 years old, had their first diagnosis of severe acute respiratory syndrome coronavirus 2 between January and February 2022, had a high risk of developing COVID-19, the severe form, and had no known contraindications to Paxlovid were all eligible to participate in the study. Regardless of whether the patients had received COVID-19 vaccinations, all patients were included in the study. The 28-day hazard ratio for severe COVID-19 and death from this condition in Paxlovid-treated patients was calculated using Cox hazard regression. Only 4737 (2.6%) of the total research participants received Paxlovid treatment, and 135,482 (75.1%) of them had an excellent COVID-19 vaccination status. Both the group that got Paxlovid (adjusted HRs: 0.54; 95% CI: 0.39–0.75) and the group that got the recommended vaccine (adjusted HRs: 0.20; 95% CI, 0.17–0.22) observed a significant decrease in the severe form of COVID-19 and deaths from it. Paxlovid appeared to be more effective in older people, those who are immunosuppressed, and patients who have an underlying neurological or cardiovascular illness. The individuals' vaccination status and Paxlovid medication did not interact significantly in this study (22).

Conclusion

In conclusion, administration of the drug combination nirmatrelvir and ritonavir is significantly linked to a decrease in the risk of hospitalization in COVID-19 outpatients, a decrease in the risk of re-hospitalization in COVID-19 hospitalized patients, and a decrease in the overall mortality of patients due to COVID-19, particularly in high-risk patients who are over 60 or have comorbidities at a younger age. It is crucial to remember that the number of patients receiving Paxlovid treatment in the present studies is minimal, and the data about them is adjusted with other data using statistical models. To monitor the real performance of nirmatrelvir-ritonavir without statistical modeling, a larger research population will be needed to more precisely assess findings such as side effects. These data collectively imply that nirmatrelvir-ritonavir may be a useful therapy option for COVID-19 individuals, particularly those who are at greater risk of developing severe illness.

Authors' contribution

Conceptualization: Alireza Amin, Mohammad Reza Moonesan.
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Validation: Alireza Amin, Mohammad Reza Moonesan.
Visualization: Alireza Amin, Shiva Maleki.

Table 1. Characteristics of included studies

Study	Study design	Study period	Number of participants		Characteristics of included patients	Paxlovid treated patients n (%)
			Total	Eligible (%)		
Wai et al (19)	Retrospective cohort	22 February 2022 to 31 March 2022	54 355	54 355 (100)	Patients in hospitals and outpatient settings who are over 60 years of age and have at least one comorbid illness with mild to moderate COVID-19	4724 (8.69)
Dryden-Peterson et al (20)	Retrospective cohort	1 January 2022 to 15 May 2022	78 474	30 322 (38.63)	Not hospitalized COVID-19 patients over 50 years old	6036 (19.90)
Shah et al (21)	Retrospective cohort	1 April 2022 to 31 August 2022	1 713 120	699 848 (40.85)	Patients with COVID-19 who are over 18 years old, are not hospitalized and have at least one comorbidity or disease that increases the chance of developing severe COVID-19	198 927 (28.42)
Saravolatz et al (22)	Retrospective cohort	1 January 2022 to 28 February 2022	595 513	180 351 (30.28)	Adolescents with COVID-19 who were over 60 years old or who had at least one disease or condition that increased the risk of severe COVID-19.	4737 (2.62)

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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