CoLab Network

Nirmatrelvir-Ritonavir for the Treatment of COVID-19

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Key Messages

The findings suggest nirmatrelvir-ritonavir reduces the risk of disease progression, hospitalization, or death compared to placebo or standard of care in people with mild to moderate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who are considered high risk but are not hospitalized. Two randomized controlled trials at a low to moderate risk of bias saw this risk reduction, though the much larger randomized controlled trial included only people who were not vaccinated.

The findings suggest nirmatrelvir-ritonavir reduces the risk of emergency department visits, hospitalization, or death compared to no treatment, or standard of care. Fourteen observational studies at a moderate to high risk of bias saw this risk reduction.

The findings suggest nirmatrelvir-ritonavir is comparable to molnupiravir or remdesivir in reducing the risk of COVID-19 hospitalization, any cause hospitalization, and death. Nineteen observational studies at a moderate to high risk of bias saw this comparability.

The incidence of mild to moderate adverse events like dysgeusia (a distorted sense of taste) or diarrhea may be higher in people who receive nirmatrelvir-ritonavir than in those who receive molnupiravir or remdesivir.

The studies lack a diverse lens, which may limit their generalizability to the Canadian population. Specifically, sex and gender are not considered, nor are people who are racialized, Indigenous Peoples, or other equity-deserving communities.

Grouping by vaccination status is not commonly reported in these studies. However, when it is reported, nirmatrelvir-ritonavir appears to be more effective in those who are partially or unvaccinated.

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Stakeholders
Two clinicians with content expertise provided comments on this report.

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Abbreviations

AE	adverse event
aHR	adjusted hazard ratio
aRR	adjusted relative risk
aOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
ED	emergency department
EHR	electronic health record
HM	hematological malignancy
IBD	irritable bowel disease
ICU	intensive care unit
NMV-r	nirmatrelvir-ritonavir
OR	odds ratio
PCR	polymerase chain reaction
PICOS	population(s), intervention(s), comparator(s), study design(s)
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SARD	systemic autoimmune rheumatic disorder
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMD	standardized mean difference
WDAE	withdrawal due to adverse event

Introduction and Rationale

In Canada, several drug treatments have received approval for the management of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The federal government, specifically the Public Health Agency of Canada, is responsible for overseeing the procurement and allocation of these drugs to ensure their availability for federal, provincial, and territorial health care systems. The following drugs, which are in high demand, are currently funded by the Public Health Agency of Canada: nirmatrelvir-ritonavir (NMV-r) (Paxlovid), remdesivir (Veklury), and tocilizumab (Actemra).

These drugs have received authorization for use in Canada and are regarded as essential tools in the management of COVID-19. To provide reliable and evidence-based guidance, CADTH has conducted comprehensive evidence reviews for NMV-r, remdesivir in patients who are hospitalized, and tocilizumab.[1] The primary objective of these reviews was to assess the available evidence on the safety, efficacy, and overall benefits of these drugs in the context of COVID-19 treatment.

In addition to the evidence reviews, CADTH has furnished implementation advice to support health care professionals in optimizing the use of NMV-r and remdesivir.[1] Specifically, this advice aimed to inform decision-making regarding the optimal utilization of NMV-r for the treatment of mild to moderate COVID-19 in adult patients who had received positive results from direct SARS-CoV-2 viral testing and were at high risk for disease progression, including hospitalization or death, when antiviral supply was limited.

Rationale
PHAC currently sources and distributes COVID-19 drugs for Canada's health care systems. Gathering postmarket evidence on their safety and efficacy is important to help determine fair access in the future.

Objective

The objective of this evidence review is to synthesize the current evidence on NMV-r, as the previous review was conducted when NMV-r was first introduced to the Canadian market (i.e., when data were limited), and the implementation advice was made in light of a supply shortage of NMV-r.

Policy Questions

1. What new evidence on the efficacy, effectiveness, and safety of NMV-r is available since the publication of the CADTH report?
2. Which patients are most likely to benefit from treatment with NMV-r?

Research Question

In adults with SARS-CoV-2 infection who are considered high risk but are not hospitalized, what is the clinical effectiveness and safety of NMV-r compared to placebo, no treatment, standard treatment, molnupiravir, or remdesivir in reducing the risk of emergency department (ED) visits, hospitalization, and mortality?

Methods

Methods
We used a systematic review approach to identify clinical trials and observational studies published from November 2021 onward. We selected studies for inclusion using criteria from the PICOS framework.

An a priori protocol was developed and registered (PROSPERO CRD42023425341) and was followed throughout the systematic review process. There were no deviations from the protocol. The protocol and systematic review followed the methods of the Cochrane Handbook for Systematic Reviews for Interventions and the PRISMA checklist for systematic reviews.[2]

Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies checklist*.[3] The complete search strategy is presented in Appendix 1. Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. The Ovid searches were run simultaneously as a multifile search and duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and

keywords. Search concepts were developed based on the elements of the population, intervention, comparator, and study design (PICOS) framework and research questions. The main search concepts were nirmatrelvir, ritonavir, and Paxlovid. The US National Institutes of Health's clinicaltrials.gov trials registry was also searched.

CADTH-developed search filters were applied to limit retrieval to all clinical trials and observational studies. The observational filter was modified to remove terms for cross-sectional studies, prevalence studies, case studies, and case reports. Retrieval was not limited by publication date but was limited to the English or French language. Conference abstracts were excluded from the search results. The initial search was completed on May 4, 2023. Regular alerts updated the database literature searches until June 19, 2023.

Eligibility Criteria

Studies that fulfilled the PICOS criteria were chosen for inclusion in this analysis. The selection process did not consider the reported outcomes as a basis for inclusion or exclusion. The specific criteria for inclusion can be found in Table 1. Studies published in November 2021 or later were included. Only studies in English or French were included.

Eligibility Criteria

Population: Outpatient adults with COVID-19.

Intervention: Nirmatrelvir-ritonavir combination therapy.

Comparator: No therapy, placebo, standard of care, remdesivir, or molnupiravir.

Table 1

Inclusion Criteria

Criteria	Description
Populations	Adults with SARS-CoV-2 infection who are considered high risk but are not hospitalized "High risk" may include the following subgroups: age (> 65 years), sex and gender, immunocompromised, number of comorbidities, Indigenous Peoples
Intervention	nirmatrelvir-ritonavir
Comparators	• Remdesivir • Inhaled glucocorticoids and/or budesonide • Molnupiravir • Usual care • No therapy • Placebo

Criteria	Description
Outcomes	Clinical effectiveness (e.g., emergency department visits, hospitalization, ICU admission, long COVID-19, rebound COVID-19, treatment adherence, time to symptom resolution) Safety (e.g., hypersensitivity, death, SAEs [i.e., grade 3 and grade 4 AEs], WDAEs)
Study designs	Completed phase II/III RCTs or higher Nonrandomized controlled clinical trials and cohort studies were included if the setting had a similar health care system as Canada, this included Australia, Greece, Italy, Denmark, Norway, Finland, Iceland, Sweden, Japan, Netherlands, New Zealand, Portugal, Spain, the UK, and the US.[a] Exclusions: Nonrandomized studies for which the settings are dissimilar to Canada, noncomparative trials, protocols for studies in progress or without results, terminated studies, registered studies in progress, editorials, letters, commentaries, conference abstracts, presentations, theses, preprints, and duplicate studies.

AE = adverse event; ICU = intensive care unit; RCT = randomized controlled trial; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WDAE = withdrawal due to adverse event.

[a] The Public Health Agency of Canada indicated a preference for results from countries with similar health care systems and context for comparability; in particular, countries with a decommodified health care system. Other countries included were high income countries in the Organization for Economic Co-operation and Development (i.e., US, UK, Australia).

Population and Subgroups

The population of interest for this systematic review is adults with COVID-19 who are not hospitalized, which includes individuals who have tested positive for COVID-19 but do not require hospitalization for their condition. The systematic review investigates various aspects of this population to gain insights into their outcomes, treatments, or interventions.

In addition to the overall population, the systematic review also identifies several subgroups of interest. They include:

- Age (> 65 years): This subgroup focuses on individuals who are 65 years or older. Age is an important factor in determining the severity and outcomes of COVID-19, as older adults tend to be at higher risk for complications.
- Sex and/or gender: This subgroup explores potential differences in COVID-19 outcomes between males and females. It aims to understand if there are any sex-based disparities in the disease's impact or response to treatments.

- Vaccination status: This subgroup examines the effects of COVID-19 in those who are vaccinated and unvaccinated. It assesses whether vaccination status influences disease severity, hospitalization rates, or other relevant outcomes.
- Immunocompromised: This subgroup includes individuals with compromised immune systems, such as those with organ transplants, undergoing chemotherapy, or with specific medical conditions. It investigates the unique challenges and risks faced by individuals who are immunocompromised and have COVID-19.
- Number of comorbidities: This subgroup focuses on individuals with multiple underlying health conditions. It aims to understand how the presence of multiple comorbidities affects the course of COVID-19 and its outcomes.
- Indigenous Peoples: This subgroup specifically considers individuals from Indigenous communities. It recognizes the potential variations in COVID-19 outcomes and health care needs within Indigenous populations.
- Populations that are more susceptible to adverse outcomes: This may be due to socioeconomic factors or disparities in health care access. It includes unhoused populations, individuals with lower socioeconomic status, rural and remote populations, racialized groups, and individuals with refugee or new immigrant status.

Intervention and Comparators

The intervention being studied in this project is NMV-r, a combination therapy used to treat COVID-19. It involves the administration of the drugs nirmatrelvir and ritonavir together.

The comparators used in this study are:

- Molnupiravir: This is an antiviral drug used for the treatment of mild to moderate COVID-19 in outpatients considered high risk.
- Remdesivir: This is another antiviral drug that has been used for the treatment of COVID-19. It is compared against NMV-r to evaluate the relative efficacy or safety of the 2 treatments.

- No therapy: This refers to the absence of any specific treatment for COVID-19. It serves as a baseline or control group to compare the outcomes of patients receiving NMV-r.
- Placebo: Placebo is an inert substance or treatment with no therapeutic effect. It is used as a comparison group to assess the specific impact of NMV-r against a nonactive intervention.
- Standard of care: This is used to describe any other care provided. This was different at different times of the pandemic, so no specific description was applied. Studies that stated that "standard of care" was the comparator were included.

Outcomes Definition

The primary outcome of interest in this systematic review is the effectiveness of the interventions being studied. This was used broadly to include many outcomes. Some outcomes of interest in this review are:

- Mortality: This was often reported at 28 day or 30 days posttreatment; however, no specific follow-up period was applied.
- ED visit without hospitalization: This outcome measures the need for individuals to seek emergency medical care for COVID-19–related symptoms or complications without requiring hospitalization.
- Hospitalization: This outcome evaluates the rate of hospital admissions among the study participants.
- Intensive care unit (ICU) admission: This outcome focuses on the need for ICU admission due to severe COVID-19 illness.
- Post–COVID-19 condition (long COVID): This outcome assesses the presence or development of long-term symptoms or complications following the resolution of acute SARS-CoV-2 infection.
- Rebound COVID-19 (at 7 days and at 30 days): This outcome examines the occurrence of a new SARS-CoV-2 infection or recurrence of symptoms within a specific time frame (7 days and 30 days) after initial recovery.
- Adherence to treatment: This outcome measures the extent to which patients adhere to the prescribed treatment regimen.

- Time to symptom resolution: This outcome assesses the duration it takes for COVID-19 symptoms to resolve completely.

In addition to effectiveness, the review also considers safety outcomes, which include:

- Death: This outcome assesses mortality rates among the study participants.
- Withdrawal due to adverse events (WDAE): This outcome evaluates the instances where participants had to withdraw from the study due to adverse events (AEs).
- Severe AEs (SAEs) refer to serious adverse events. This outcome focuses specifically on SAEs of grade 3 and grade 4 severity.
- Hypersensitivity: This outcome measures the occurrence of hypersensitivity reactions to the interventions being studied.

Study Designs

The study designs included in this systematic review are:

- Completed phase II/III randomized controlled trials (RCTs) or higher: This refers to studies that have completed randomized controlled trials, including those conducted in phase II or phase III or higher stages of clinical research.
- Nonrandomized controlled clinical trials: This category includes the comparison of intervention groups and control groups, but without the random assignment of participants. However, the assignment to intervention or control is still completed under experimental design (e.g., the assignment of intervention or control follows a research protocol).
- Observational studies: These study designs involve the comparison of intervention groups and control groups, but without the experimental assignment of participants. This means that participants received intervention or control due to factors like timing in the pandemic, physician preference, and patient preference that were not due to a research protocol. Additionally, the review includes only observational studies from countries

with a similar health care system as Canada, such as Australia, Greece, Italy, Denmark, Norway, Finland, Iceland, Sweden, Japan, Netherlands, New Zealand, Portugal, Spain, the UK, and the US.

Exclusions from the review criteria are:

- Nonrandomized studies or observational studies completed in health care settings dissimilar to Canada: Studies from countries other than Australia, Greece, Italy, Denmark, Norway, Finland, Iceland, Sweden, Japan, Netherlands, New Zealand, Portugal, Spain, the UK, and the US are excluded from the review.
- Noncomparative studies: Studies that lack a comparison group or control group are excluded.
- Protocols for studies in progress or without results: Protocols for ongoing studies or studies without reported results are excluded.
- Terminated studies: Studies that have been terminated prematurely are excluded.
- Registered in-progress studies: Ongoing studies that are registered but have not yet reported results are excluded.
- Editorials, letters, commentaries, conference abstracts, presentations, theses, preprints: These types of publications or formats are excluded from the review.

Study Selection Process

Two independent reviewers screened a sample of 10 abstracts identified during the literature search based on the inclusion criteria in Table 1. Subsequent samples of 10 abstracts were screened until a 90% or more agreement was reached. Then each of the remaining abstracts were screened by 1 of the reviewers. Abstracts selected for inclusion by either reviewer proceeded to full-text review.

A similar calibration exercise was undertaken for the full-text review. Random samples of 5 full texts were reviewed by 2 independent reviewers until a 90% or more agreement was reached. The remaining full texts were each screened by 1 of the reviewers. Disagreements on final inclusion were resolved through consensus and discussion, and where required, a third reviewer was consulted.

Data Extraction and Risk of Bias Assessment

For all included studies, single reviewers extracted data, including the year of publication, country, study design, patient characteristics, comparator type, and reported outcomes (Appendix 2), using a standardized data extraction form.

The quality of RCTs was assessed using the revised Cochrane Collaboration's Risk of Bias tool (ROB v. 2.0).[4] Each RCT was assessed using 5 criteria broadly covering the areas of randomization, deviation from intended intervention, missing outcome data, measurement of outcome, and selection of reporting the result. Each criterion was assigned a rating of "low," "some," or "high" concern.[4]

The nonrandomized studies were evaluated using the Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool.[5] The assessment was based on the following parameters: bias due to confounding, selection bias, bias in classification, bias due to deviations from intended interventions, bias due to missing data, bias in measurement, and reporting bias. Each criterion was assigned a rating of "low," "moderate," "serious," or "critical" risk of bias.[5] Single reviewers conducted quality assessment, and discrepancies were resolved through discussion. Studies were not excluded based on the outcome of the quality assessment.

In the context of these tools, ratings are used to classify the level of bias as high risk, concern, critical, and other. It is important to note that assigning a high-risk rating to a specific domain implies an overall rating of high risk.

Data Analyses and Synthesis

Due to substantial heterogeneity in study comparators, population, and outcomes, a meta-analysis was not undertaken. The approach to data analysis was narrative.

For results summary tables, where study reports did not provide effect estimates specific to the outcomes and treatment comparisons of interest, but did report requisite frequency or rate data, relative proportions, relative risks (RRs), and odds ratios (ORs) were calculated by the research team and corresponding 95% confidence intervals (CIs) were estimated from standard errors approximated from these data.

Results of Clinical Evaluation

Selection of Primary Studies

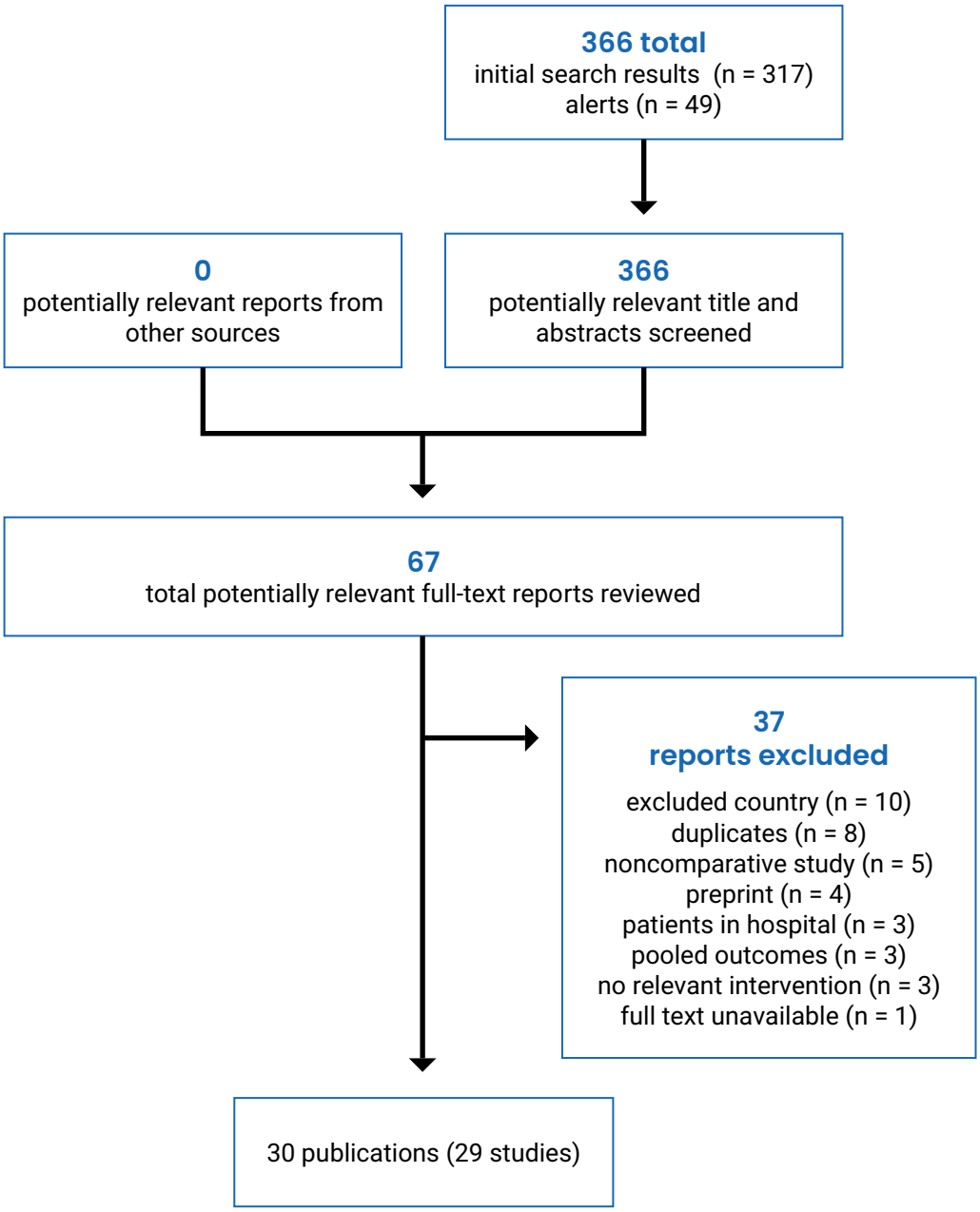
The search strategy yielded 366 unique citations, 299 of which were excluded after abstract review. Sixty-seven studies proceeded to full-text review. A total of 37 studies were excluded for the following reasons: not a country of interest (n = 10); duplicates (n = 8); noncomparative study (n = 5); preprint (n = 4); patients were hospitalized (n = 3); pooled outcomes (n = 3); no relevant intervention (n = 3); and no full text available (n = 1).

Twenty-nine unique studies across 30 publications were included in the final analysis (Figure 1).

Included Studies
Twenty-nine unique studies across 30 publications are included in the final analysis: 2 RCTs across 3 publications, and 27 observational studies.

Figure 1

PRISMA Flow Chart of Selected Reports



Study and Patient Characteristics

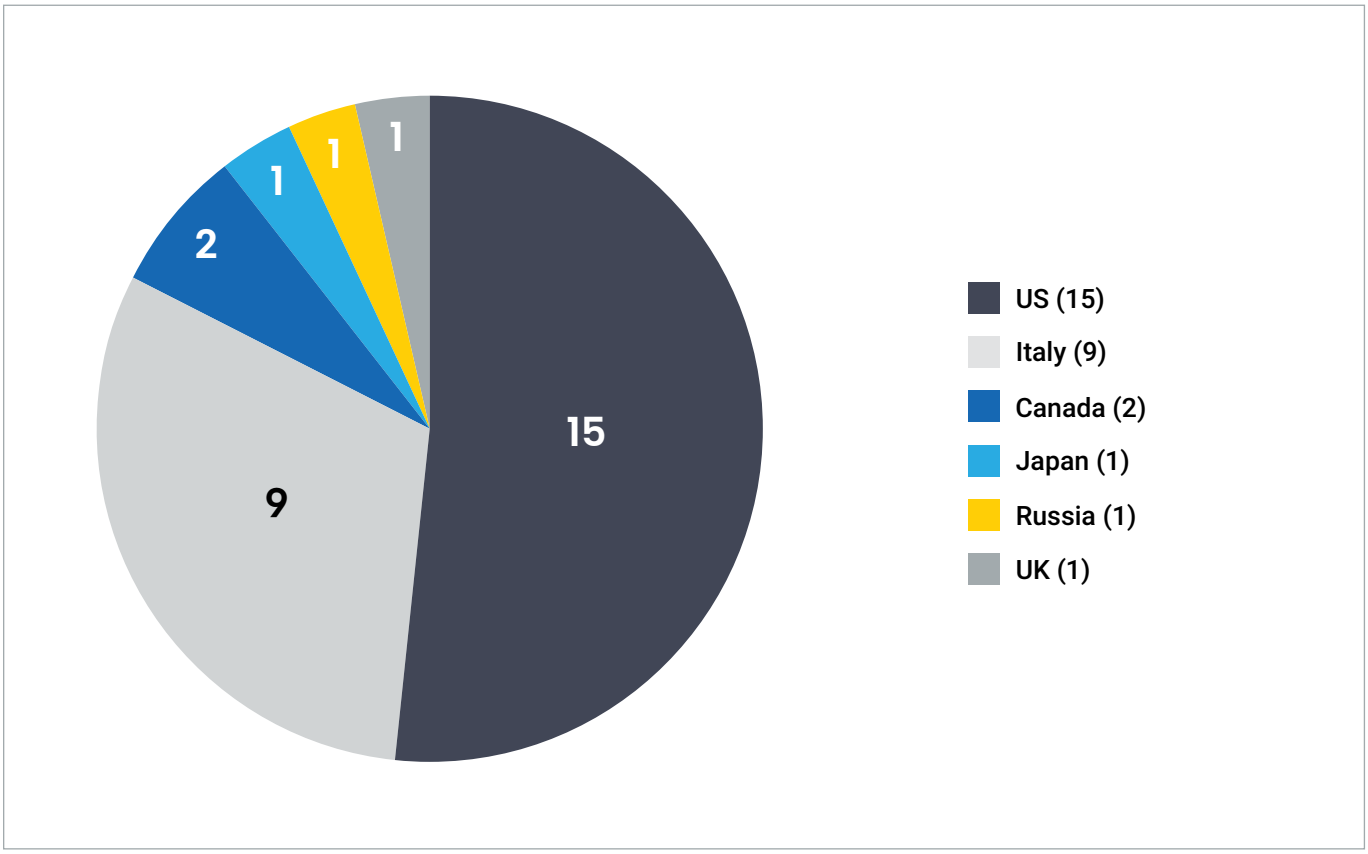
Twenty-nine studies across 30 publications were included in the final dataset: 2 RCTs across 3 publications, and 27 observational studies (Figure 1). One of the RCTs was a global study that recruited participants from 21 countries and was led by the UK[6] and the second was conducted in Russia.[7] The RCT led by the UK was conducted during the Delta wave, and the RCT from Russia did not specify which variant was predominant at the time of study. Authors in 56% of the observational studies specified that the studies were conducted when the Omicron wave and its subvariants were predominant.

Overall, more than half of the included studies were conducted in the US (n = 15), followed by Italy (n = 9), and Canada (n = 2) (Figure 2). One study each was conducted in Japan and Russia. One RCT recruited participants from 21 countries and was led by the UK (Figure 2).

Key Point
Fifty-six percent of the included observational studies collected data during the Omicron wave.

Figure 2

Number of Included Studies by Country



Note: The Hammond randomized controlled trial was led by researchers in the UK. This randomized controlled trial was a global study and recruited patients from 21 countries: the US (105 sites), Bulgaria (30 sites), South Africa (28 sites), Brazil (26 sites), India (19 sites), Mexico (18 sites), Ukraine (17 sites), Turkey (16 sites), Japan and Spain (10 sites each), Russia (9 sites), Argentina and Colombia (8 sites each), Poland and South Korea (7 sites each), Hungary (6 sites), Taiwan (5 sites), Malaysia and Czech Republic (4 sites each), and Thailand and Puerto Rico (3 sites each).

The 2 included RCTs compared NMV-r to placebo[6,8] and standard treatment,[7] respectively. Nineteen of the observational studies included only 1 comparator group, while the remaining 8 observational studies included 2 or more comparator groups. Twenty-two observational studies did not focus on any specific subgroup; these studies compared NMV-r to no treatment (n = 7),[9-15] no NMV-r (n = 4),[16-19] molnupiravir (n = 10),[15,20-28] and remdesivir (n = 4),[20,22,23,25] and one study compared NMV-r and standard treatment.[28]

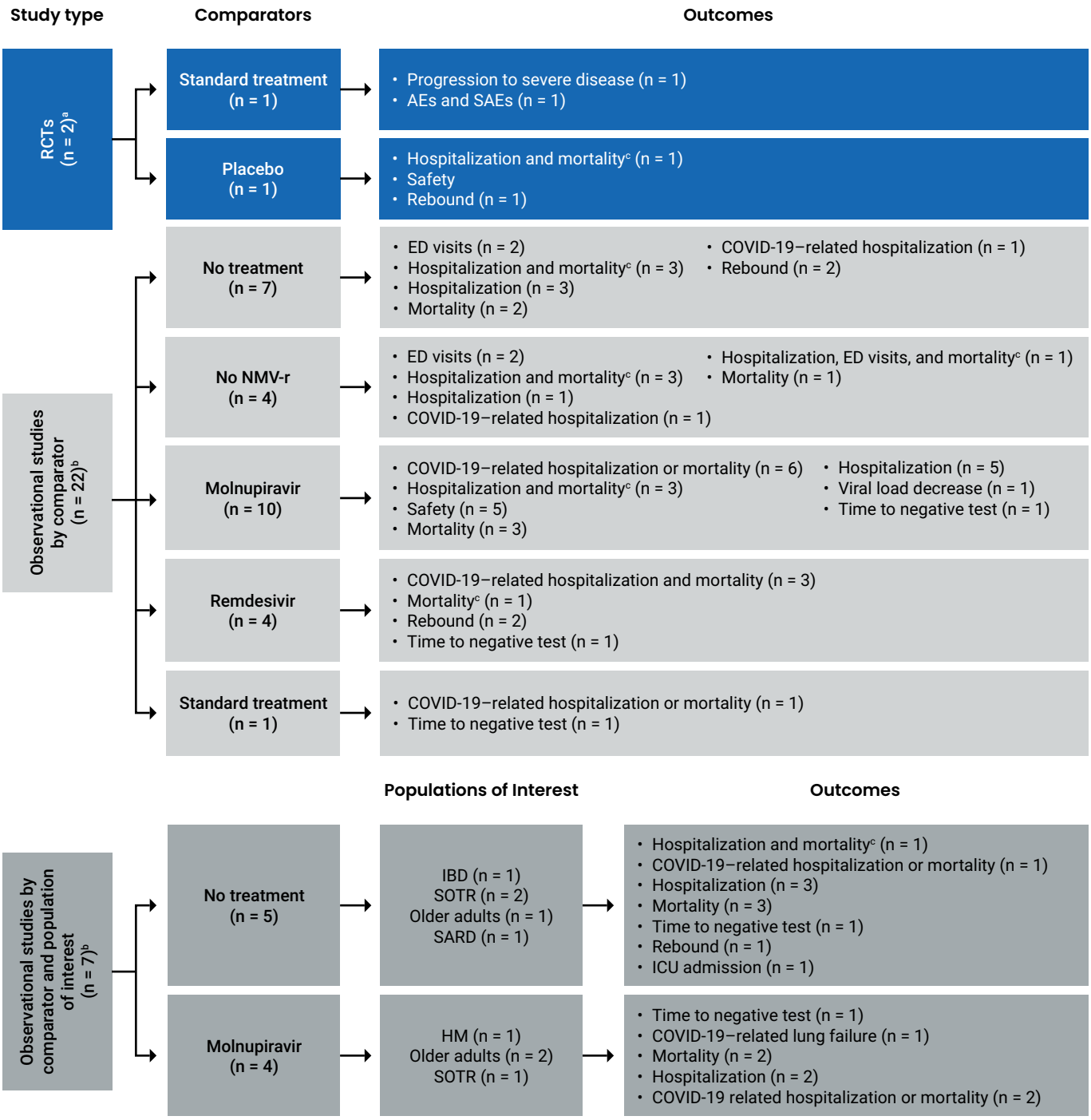
The remaining 7 studies focused on specific population of interest at high risk of progression to severe COVID-19. Two studies each focused on older adults[29,30] and recipients of a solid organ transplant.[31,32] One study each focused on individuals with irritable bowel disease (IBD),[33] individuals with hematological malignancies (HMs),[34] and individuals with systemic autoimmune rheumatic disorders (SARD).[35] Across these studies, NMV-r was compared to no treatment (n = 55)[30-33] and to molnupiravir (n = 4)[29,30,32,34] (Figure 3).

Outcomes reported across studies included ED visits, COVID-19–related hospitalization, any cause hospitalization, mortality, safety, rebound, viral load decrease, ICU admission, disease progression, and time to negative test (Figure 3).

Individuals who received NMV-r had 1 or more risk factors for progression to severe COVID-19. The risk factors identified across studies were age, immunocompromised status, body mass index (BMI) higher than 25, presence of at least 1 comorbid illness (e.g., diabetes, chronic heart disease), smoking status, race, and ethnicity. In some observational studies, an inclusion criterion was a laboratory-confirmed COVID-19 diagnosis (i.e., polymerase chain reaction [PCR] test). However, other studies that conducted a retrospective analysis of electronic health records (EHRs) noted that many study participants who received a prescription for NMV-r or antivirals did not have a laboratory-confirmed COVID-19 diagnosis (i.e., positive PCR test) within their EHRs.

Figure 3

Number of Included Studies by Comparator, Population of Interest, and Outcomes



AE = adverse event; ED = emergency department; HM = hematological malignancy; IBD = irritable bowel disease; ICU = intensive care unit; NMV-r = nirmatrelvir-ritonavir; RCT = randomized controlled trial; SAE = serious adverse event; SARD = systemic autoimmune rhematic disorder; SOTR = recipient of a solid organ transplant.

[a] Two RCTs across 3 publications.

[b] Unique studies. Eight studies included more than 1 comparator.

[c] Composite outcomes.

Randomized Controlled Studies

The first RCT[7] (Balykova et al., 2022) was a multicenter study conducted in Russia. The risk of bias due to the randomization process and deviation from the intended intervention was of some concern. However, in all other domains, the risk of bias was low. Therefore, the overall assessment of the study's bias risk was of some concern, (Table 2). Limitations of this study include that in addition to NMV-r, the intervention group also received unspecified pathogenic and symptomatic therapy. The lack of detailed information about the specific pathogenic and symptomatic therapies administered to the intervention group raises questions about their potential impact on the outcomes of interest. Without a clear understanding of these additional treatments, it becomes challenging to differentiate the effects of NMV-r from those of concurrent therapies. This makes it difficult to ascertain the true efficacy and isolates the specific contributions of the NMV-r intervention in the study (Table 2).

Summary
The 2 included RCTs report on different outcomes: 1 assessed hospitalization and death and the other reported disease progression. One included only those who were unvaccinated. This makes comparison difficult.

Findings Suggest
Nirmatrelvir-ritonavir reduces progression to severe COVID-19 when compared to standard therapy. Before treatment, 68% of the study population had comorbidities, and 75% had risk factors for severe progression.

Table 2

Risk of Bias Assessment — Strengths and Limitations of Balykova et al., 2022

Author Year	Risk of bias						Strengths	Limitations
	D1	D2	D3	D4	D5	Overall		
Balykova 2022 [7]	−	−	+	+	+	−	Adequate method of randomization, nonsubjective outcomes including SARS-CoV-2 tests and mortality	Insufficient description of therapies received by control and intervention groups.

Domains
D1: Bias arising from the randomization process, **D2:** Bias due to deviations from intended intervention, **D3:** Bias due to missing outcome data, **D4:** Bias in measurement of the outcome, **D5:** Bias in selection of the reported result.

Judgement
+ Low − Moderate x High ! Critical ? Unclear

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

This RCT assessed the safety (frequency of AEs and SAEs) and efficacy (progression to severe disease) of NMV-r in individuals with SARS-CoV-2 infection compared to standard therapy.[7] The study included 264 adults who were not hospitalized (132 intervention, 132 control) and were aged 18 years to 80 years with mild to moderate symptomatic COVID-19 infection and onset of symptoms less than 5 days before randomization. Patients with renal insufficiency or liver failure, those who were vaccinated less than 4 weeks prior, and/or those who had received direct acting antivirals within 10 days before screening were excluded. In the intervention group, patients received NMV-r twice a day for 5 days plus pathogenic and symptomatic therapy, while the control group received standard therapy in accordance with the interim guidelines in force at the time of the study. Visits were conducted either in person or by phone call for examinations, vital signs, and symptom scores up to 29 days after randomization. Clinical status, including worsening or improvement assessed on a categorical ordinal scale, and proportion of patients who were SARS-CoV-2 ribonucleic acid (RNA) negative, were recorded at visits 2, 3, and 4. Symptom scores for visits 2 to 6 were also recorded on the COVID-19 Major Symptom Rating scale.[7]

At baseline, 68% of randomized patients had comorbidities, including hypertension, and kidney and respiratory diseases, while 75% had risk factors for progression to severe COVID-19.[7] Risk factors of progression to severe disease such as age, obesity, and prevalence of comorbidities were similar in both groups. By day 16, no patient in the intervention group progressed to severe COVID-19, compared to 8 patients in the control group ($P < 0.0275$). By day 6, 35.6% of patients in the intervention group achieved complete recovery, compared to 14.4% of the control group ($P = 0.0001$), and 82.58% of patients in the intervention group were SARS-CoV-2 RNA negative, which was 20% higher than the control group ($P < 0.0001$).[7]

No SAEs, WDAEs, or deaths occurred during the study period.[7] AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and included gastrointestinal disorders (diarrhea, dry mouth, nausea), laboratory and instrumental data (increased alanine aminotransferase and aspartate aminotransferase levels),

skin and subcutaneous tissue disorders (erythema), and nervous system disorders (dysgeusia). Ten patients (7.6%) in the intervention group and 8 patients (6%) in the control group experienced mild to moderate AEs, including increased alanine aminotransferase and aspartate aminotransferase levels, dysgeusia, diarrhea, and dry mouth. All AEs were transient and did not require changes in the treatment regimen. No statistically significant differences in AEs in terms of the presence, severity, and causal relationship with therapy and outcomes between those treated with NMV-r and the control group were observed.[7]

The second RCT, by Hammond et al., 2022, enrolled participants from 343 worldwide sites across 21 countries and was led by the UK.[6] The risk of bias from all domains, including randomization, deviation, missing data, outcome measurement, and reporting, were low. The overall risk of bias for this study was low (Table 3). An important limitation of this study was its restriction to patients who were not vaccinated (Table 3).

Findings Suggest
Nirmatrelvir-ritonavir reduces COVID-19 hospitalization or death when treatment is started within 3 to 5 days of symptom onset when compared to a placebo in those who are unvaccinated.

Table 3

Risk of Bias Assessment — Strengths and Limitations of Hammond et al., 2022

Author Year	Risk of bias						Strengths	Limitations
	D1	D2	D3	D4	D5	Overall		
Hammond 2022 [6]	+	+	+	+	+	+	Included patients from diverse regions, enabling broad geographic generalizability; nonsubjective outcomes including hospitalization and mortality	Trial was restricted to patients who were not vaccinated

Domains
D1: Bias arising from the randomization process, **D2:** Bias due to deviations from intended intervention, **D3:** Bias due to missing outcome data, **D4:** Bias in measurement of the outcome, **D5:** Bias in selection of the reported result.

Judgement
+ Low − Moderate x High ! Critical ? Unclear

This RCT assessed the efficacy (COVID-19 hospitalization or all-cause mortality), viral load decrease (at baseline, and days 3, 5, 10, and 14), and safety of NMV-r (SAEs and WDAEs up to day 34) in adult outpatients who were not vaccinated and had symptomatic COVID-19 at high risk of progression to severe disease compared to placebo.[6]

The study included 2,246 adults (1,120 intervention and 1,126 control) with confirmed infection and symptom onset fewer than 5 days before randomization, and at least 1 risk factor for progression to severe COVID-19.[6] Patients with previous SARS-CoV-2 infection or hospitalization and those who had received COVID-19 plasma treatment or a SARS-CoV-2 vaccine were excluded. Patients in the intervention group received NMV-r every 12 hours for 5 days, while those in the control group received placebo. Prespecified subgroup analyses were conducted on patients who started treatment within 3 and 5 days of symptom onset. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0, and incidence data were provided for each treatment group on all patients who received at least 1 dose of NMV-r or placebo through day 34.[6]

The median age of the study population was 46 years.[6] Overall, 51% were male, 71.5% were white, and 14% identified as Asian. Conditions associated with the risk of progression to severe COVID-19 at baseline were BMI of 25 or higher (80.5%), current smoking (39%), and hypertension (33%). Most patients (93.8%) had not received monoclonal antibodies for COVID-19 treatment at randomization. Risk factors were similar in both the intervention and control groups.[6]

Statistically significantly fewer patients who commenced treatment within 3 days of symptom onset in the intervention group had COVID-19 hospitalization or death after 28 days, compared to placebo, a difference of −5.81% (95% CI, −7.78 to −3.84; $P < 0.001$), and a RR reduction of 88.9%.[6] For patients who commenced treatment within 5 days of symptom onset, the RR reduction of COVID-19 hospitalization or death through day 28 was 87.8% ($P < 0.001$). Viral load detection was assessed at baseline and day 5 in 70% of patients. After adjusting for baseline viral load, serology

status, and geographic location, NMV-r statistically significantly reduced viral load at day 5 by a factor of 10 compared to placebo.[6]

The incidence of AEs was similar in both the intervention group (22.6%) and the control group (23.9%).[6] Nonserious AEs (i.e., grade 1 and 2) that resolved included dysgeusia, diarrhea, increased fibrin D-dimer, increased alanine aminotransferase, headache, decreased creatine renal clearance, and vomiting. Nonserious AEs considered by site investigators to be related to the trial or placebo drug were more common in the intervention group (7.8%) compared to the control group (3.8%) and were largely attributed to dysgeusia (4.5% versus 0.2%) and diarrhea (1.3% versus 0.2%). All AEs were resolved except 1 case of grade 3 dysgeusia.[6]

Fewer grade 3 or 4 AEs were reported in the intervention group compared to the control group (4.1% versus 8.3%), as well as fewer SAEs (1.6% versus 6.6%) and WDAEs (2.1% versus 4.2%).[6] The most SAEs occurring in at least 2 patients were COVID-19 pneumonia in 6 patients in the NMV-r group compared to 37 in the placebo group (0.5% versus 3.3%) and decreased renal creatine clearance (2 patients [0.2%] compared to 3 [0.3%]); however, none were considered by the investigator to be related to NMV-r or placebo. By day 34, no SAE resulted in death in the intervention group. Thirteen patients died in the placebo group, and all deaths were related to COVID-19. Twelve patients had a life-threatening (grade 4) AE (2 patients in the intervention group and 10 in the control group). Among patients with WDAEs, most events were mild to moderate and resolved at the time of analysis. Few events (≤ 0.8%) leading to discontinuation of the study drug or placebo were considered by the investigator to be related to the trial drug or placebo.[6]

Additional results from this trial on the occurrence of viral load rebound were published in another study.[8] From baseline to day 14, rebound occurred in 23 of 990 patients (2.3%) in the intervention group and 17 of 980 (1.7%) in the control group. The incidence of viral load rebound was similar in both groups irrespective of coexisting illnesses, NMV-r exposure, hospitalization, death, or moderate to severe COVID-19 symptoms.[8]

Discussion

Findings from the 2 included RCTs suggest that NMV-r compared to placebo or standard treatment statistically significantly reduces the risk of COVID-19–related hospitalization, progression to severe COVID -19, and all-cause mortality in adult outpatients with mild to moderate SARS-CoV-2 infection who are considered high risk. However, these outcomes were only studied in 1 RCT each and in different populations. The incidence of COVID-19 rebound was similar in both the NMV-r and placebo groups. Patients in the NMV-r group had a statistically significantly faster time to symptom resolution, a larger proportion of patients achieving complete recovery by day 6, and a negative SARS-COV-2 RNA analysis compared to standard therapy.

Key Point
RCT findings suggest that nirmatrelvir-ritonavir reduces the risk of hospitalization, progression to severe disease, and all-cause death in outpatient adults with mild to moderate infection who are high risk. Interpret with caution.

The studies also demonstrated the safety of NMV-r. SAEs were rare and occurred less frequently in patients who received NMV-r compared to those who received placebo. Among patients who experienced WDAEs, the events were mostly mild to moderate, with less than 1% of the WDAEs considered by investigators to be related to NMV-r or placebo.

Key Point
RCT findings suggest that severe AEs are rare, and AEs are mild to moderate and transient after treatment with nirmatrelvir-ritonavir.

Some limitations may impact the generalizability of these results. In the first study, patients in the NMV-r group also received unspecified pathogenetic and symptomatic therapy. The effect of this additional therapy in ameliorating COVID-19 symptoms in the intervention group is unknown. The second RCT recruited patients who were unvaccinated from 343 sites worldwide. This patient group may not be representative of the current population in Canada, in which in which more than 80% of eligible individuals have completed their primary vaccination series.

Limitations
The Russian study included an additional unspecified therapy in the treatment group. The UK study was restricted to those who were unvaccinated. This may affect the generalizability of the findings.

Observational Studies

NMV-r Versus No Treatment

Seven observational studies compared NMV-r to no treatment. All 7 studies were conducted in the US. Five of the studies were assessed as having a moderate risk of bias,[9-11,14,15] 1 was at serious risk of bias,[13] and 1 was at a critical risk of bias (Table 4).[12] Three studies reported on the composite outcome of hospitalization and mortality, 3 studies reported on any cause hospitalization, 2 studies reported on mortality, 2 studies reported on ED visit outcomes, 2 studies reported the incidence of rebound infection, 1 study reported on COVID-19–related hospitalization, and 1 reported the time to viral and symptom clearance (Table 5).

Summary
Seven observational studies compared nirmatrelvir-ritonavir to no treatment. A meta-analysis was not possible because of the differences across the studies.

Table 4

Risk of Bias Assessment — Strengths and Limitations of Studies Comparing NMV-r to No Treatment

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Aggarwal 2022 [10]	−	+	+	+	?	+	+	−	Objective endpoints (hospitalization, mortality), propensity score matched	High proportion of patients who received NMV-r did not have laboratory test results, possible residual confounders
Al-Obaidi 2022 [11]	−	+	+	?	?	+	?	−	Objective endpoints (hospitalization), matched groups	Potential residual confounders (e.g., socioeconomic status, biomarkers not captured in EHRs)
Bajema 2022 [15]	−	+	+	+	+	+	+	−	Matched groups, incorporated Veteran Affairs EHR data	Unable to ascertain symptom onset
Dryden-Peterson 2023 [14]	−	+	+	+	+	+	+	−	Inverse probability weighting to balance treatment and control groups	Inability to assess treatment adherence, potential residual confounding and selection bias

Author Year	Risk of bias	Strengths	Limitations
Epling 2022 [13]	D1 (x) D2 (+) D3 (+) D4 (?) D5 (+) D6 (?) D7 (?) Overall (x)	Objective endpoints (nasal swabs, biomarkers)	Small sample size n = 15
Pandit 2023 [12]	D1 (x) D2 (+) D3 (+) D4 (x) D5 (x) D6 (?) D7 (?) Overall (!)	Vital information on COVID-19 rebound	Unbalanced sample size, largely white population, 31% of consented participants excluded due to missing data
Shah 2023 [9]	D1 (-) D2 (+) D3 (-) D4 (+) D5 (-) D6 (+) D7 (-) Overall (-)	Objective endpoints (hospitalization), highlights underutilization of NMV-r	Inability to assess treatment adherence, dates used may not reflect symptom onset, asymptomatic individuals included in comparison group may bias results

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results.

Judgement

(+) Low (-) Moderate (x) High (!) Critical (?) Unclear

EHR = electronic health record; NMV-r = nirmatrelvir-ritonavir.

Risk of Bias

Five of the studies are at moderate risk of bias, 1 is at serious risk of bias, and 1 is at critical risk of bias.

Table 5

Reported Effect Measures by Subgroups in Studies Comparing NMV-r to No Treatment

First author, year	Overall outcomes	< 60 years	≥ 60 years	Vaccinated	Unvaccinated	Comorbidities	Without comorbidities
Mortality							
Aggarwal, 2023[10]	aOR = 0.15 (95% CI, 0.03 to 0.50)[a]	NR	NR	NR	NR	NR	NR
Bajema, 2022[15]	RR = 0.21 (95% CI, 0.09 to 0.52)[a]	NR	NR	NR	NR	NR	NR
All-cause hospitalization							
Aggarwal, 2023[10]	aOR = 0.45 (95% CI, 0.33 to 0.62)[a]	aOR = 0.53 (95% CI, 0.34 to 0.80)[a]	aOR = 0.37 (95% CI, 0.23 to 0.57)[a]	aOR = 0.47 (95% CI, 0.29 to 0.74)[a]	aOR = 0.46 (95% CI, 0.27 to 0.77)[a]	≥ 2 aOR = 0.37 (95% CI, 0.25 to 0.654)[a]	0 to 1 comorbidities aOR = 0.68 (95% CI, 0.41 to1.12)
Bajema, 2022[15]	RR = 0.66, (95% CI, 0.48 to 0.91)[a]	NR	NR	NR	NR	NR	NR
Shah, 2023[9]	aHR = 0.45, (95% CI, 0.43 to 0.48)[a]	Aged 18 to 49 aHR = 0.59 (95% CI, 0.48 to 0.71)[a] Aged 50 to 64 aHR = 0.40 (95% CI, 0.34 to 0.58)[a]	AHR = 0.53 (95% CI, 0.48 to 0.58)[a]	3 doses: aHR = 0.50 (95% CI, 0.45 to 0.55)[a] 2 doses aHR = 0.50 (95% CI, 0.42 to 0.58)[a]	aHR = 0.50 (95% CI, 0.43 to 0.59)[a]	1 aHR = 0.57 (95% CI, 0.45 to 0.71)[a] ≥ 2 aHR = 0.47 (95% CI, 0.44 to 0.51)[a]	aHR = 0.89 (95% CI, 0.58 to 1.36)
COVID-19–related hospitalization							
Aggarwal, 2023[10]	aOR = 0.40 (95% CI, 0.28 to 0.57)[a]	NR	NR	NR	NR	NR	NR
Composite outcome of hospitalization and mortality							
Al-Obaidai, 2023[11]	OR = 0.42 (95% CI, 0.30 to 0.58)[a]	OR = −0.8 (95% CI, −1.3 to −0.3)[a]	OR = −1.9 (95% CI, −2.9 to −0.9)[a]	OR = −1.0 (95% CI, −1.7 to −0.4)[a]	OR = −1.2 (95% CI, −3.1 to −1.0)[a]	NR	NR
Bajema, 2022[15]	RR = 0.53 (95% CI, 0.39,0.72)[a]	NR	NR	NR	NR	NR	NR

First author, year	Overall outcomes	< 60 years	≥ 60 years	Vaccinated	Unvaccinated	Comorbidities	Without comorbidities
Dryden-Peterson,[b] 2022[14]	RR = 0.56 (95% CI, 0.42 to 0.75)[a]	RR = 0.55 (95% CI, 0.30 to 1.03)	RR = 0.55 (95% CI, 0.40 to 0.77)[a]	RR = 0.69 (95% CI, 0.50 to 0.94)[a]	RR = 0.19 (95% CI, 0.08 to 0.49)[a]		
Viral and symptom rebound							
Pandit, 2022[12]	OR = 1.52 (95% CI, 0.51 to 5.05)[a]	NR	NR	NR	NR	NR	NR
Epling, 2022[13]	RR = 1.00 (95% CI, 1.00 to 1.00)	NR	NR	NR	NR	NR	NR

aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CI = confidence interval; NMV-r = nirmatrelvir-ritonavir; NR = not reported; OR = odds ratio RR = relative risk.

[a]Statistically significant.

[b]Stratification by age was based on individuals aged 50 to 64 years and those 65 years or older.

The first study[10] (Aggarwal et al., 2022) was a retrospective propensity score matched-cohort study of adults with records in the statewide Colorado health system. The overall risk of bias in this study was moderate (Table 4). The study compared 28-day COVID-19–related hospitalization, any cause hospitalization, mortality, and ED visit outcomes between patients who received NMV-r and those who received no COVID-19 treatments within 10 days of a positive test. Among those who met the inclusion criteria, 7,168 patients who received NMV-r were matched to 9,361 untreated patients. Covariates with high standardized mean differences (SMD) (> 0.1) post matching included age, immunocompromised status, and the number of comorbidities. Regression models were adjusted for age, sex, race and ethnicity, insurance status, obesity, immunocompromised status, number of vaccination doses, number of comorbid conditions, and Omicron variant status. Receipt of NMV-r was associated with a statistically significantly reduced risk of 28 day all-cause hospitalization (adjusted odds ratio (aOR) = 0.45; 95% CI, 0.33 to 0.62; P < 0.0001), mortality (aOR = 0.15; 95% CI, 0.03 to 0.50; P = 0.0010), and ED visits (aOR = 0.74; 95% CI, 0.63 to 0.87; P = 0.0002) compared to no treatment.[10] Study limitations include the

high proportion of patients who received NMV-r with no documented positive SARS-CoV-2 test, and potential residual confounding from unmeasured characteristics associated with high risk of COVID-19 but not captured in EHRs (Table 4).[10]

The second study[11] (Al-Obaidi et al., 2022) was a retrospective propensity score matched cohort study assessed as having at a moderate risk of bias (Table 4). The study compared the composite outcome of 30-day all-cause hospitalization and mortality, and 30-day ED visits as a secondary outcome, in a propensity score matched cohort of patients who received NMV-r (5,754) with patients who received no treatment (5,754) for confirmed SARS-CoV-2 infection. All post matching SMD covariates, including age, BMI, vaccination status, race, and comorbidities were below P = 0.05, indicating no significant difference between the 2 groups at baseline. Compared to the untreated group, the proportion of patients with the composite outcome was statistically significantly reduced in the NMV-r group, a difference of −1.2% (95% CI, −1.7 to −0.8; P < 0.01). NMV-r was also associated with statistically significantly reduced rates of all-cause hospitalization of −1.2% (95% CI, −1.6 to −0.7; P < 0.01); however, no statistically significant difference in mortality was observed between the NMV-r and the no treatment control groups. In subgroup analysis of the primary composite outcome, receipt of NMV-r was statistically significantly associated with reducing the risk of hospitalization and mortality regardless of age group (≥ 65 years versus < 65 years) or vaccination status; NMV-r also statistically significantly reduced ED visits by −1.0% (95% CI, −1.6 to −0.3; P < 0.01). Limitations of this study include potential residual confounding from unmeasured characteristics (e.g., socioeconomic status) not captured in EHRs (Table 4).[11]

The third study[15] (Bajema et al., 2022) was conducted in the US and assessed the effectiveness of NMV-r compared to no treatment in reducing the risk of 30-day all-cause hospitalization or death in patients who were considered at risk and had confirmed COVID-19 with records in the Veterans Health Administration database. Participants were first matched based on National Institutes of

Health tier of prioritization for anti-SARS-CoV-2 therapies, VA Integrated Service Network, and calendar time, then by propensity scores estimated based on additional factors selected a priori to be associated with both the exposure and outcome. The study was assessed as having a moderate risk of bias (Table 4). Records of veterans who tested positive for COVID-19 and received NMV-r were matched to those who received no treatment (1,587 participants in each arm). Overall, 90% of participants were male, the median age was 54 years, 70% to 72% were white, patients had a median of 4 risk factors associated with severe COVID-19, and 26% of participants were unvaccinated. Compared to no treatment, participants who received NMV-r had a statistically significantly lower risk of death (risk ratio = 0.21; 95% CI, 0.09 to 0.52) and hospitalization (risk ratio = 0.66; 95% CI, 0.48 to 0.91). Among participants who were alive at day 31, no further statistically significant reductions in 31-day to 180-day incidence of hospitalization (sub hazard ratio = 1.07; 95% CI, 0.83 to 1.37) or death (hazard ratio = 0.61; 95% CI, 0.35 to 1.08) were observed. Study limitations include the inability to assess true symptom onset and prior infections, which may provide background immunity and impact the effectiveness of antiviral treatment. In addition, patients were predominantly male (90%) and the capture of outpatient outcomes, including hospitalizations and COVID-19 treatments, may be incomplete.[15]

The fourth study[14] (Dryden-Peterson et al., 2023) was a population-based cohort study that used inverse probability-weighted analysis based on a priori selected factors determined to be associated with treatment. It utilized patient data from Massachusetts and southern New Hampshire and was assessed as having a moderate risk of bias (Table 4). The study compared the composite outcome of hospitalization or mortality in 12,541 (28.1%) adults aged 50 years or older who received NMV-r with 32,010 patients (71.9%) who received no antiviral treatment for confirmed SARS-CoV-2 infection. Overall, most patients had received 3 or more vaccine doses (90.3%). At baseline, patients who received NMV-r were older, had more comorbidities, and had a higher vaccination rate. Receipt of NMV-r was associated with a statistically significantly

reduced risk of hospitalization or mortality (aOR = 0.56; 95% CI, 0.42 to 0.75). Study limitations include potential residual confounding due to differential access to COVID-19 vaccines, diagnostic tests, treatment, and unmeasured adherence to NMV-r, which could result in underestimation of efficacy.[14]

In the fifth study[13] (Epling et al., 2022), viral sequencing and culture analysis, serologic assays, T-cell simulation assays, and soluble biomarkers were performed on plasma samples collected from adult participants evaluated at the National Institutes of Health.[13] The study was assessed as having a serious risk of bias (Table 4). This study aimed to evaluate the rebound of SARS-CoV-2 infection in patients who had received NMV-r treatment (n = 6), patients with rebound symptoms with no receipt of prior antiviral therapy (n = 2), and patients with acute Omicron infection (n = 7). Among patients with rebound after NMV-r, rebound occurred 12.5 days after initial symptom onset and 6.5 days after completing treatment. Of the 8 patients with rebound, none developed severe symptoms or required additional therapy. Robust cytokine-producing, proliferating, activated SARS-CoV-2–specific T-cell responses were greater than those with acute COVID-19, along with rising T-cell counts in patients who rebounded. Findings suggest that rebound is associated with a more robust immune response rather than uncontrolled viral replication. A limitation of this study was its small sample size and no adjustment for confounding.[13]

The sixth study[9] (Shah et al., 2023) retrospectively assessed the 30-day risk of hospitalization among 198,927 (28.4%) adults who received NMV-r compared to 500,921 (71.6%) who did not receive any antiviral therapy within 5 days of COVID-19 diagnosis.[9] The risk of bias in this study was assessed as moderate (Table 4). At baseline, the prevalence of comorbidities was similar in both groups. Overall, the receipt of NMV-r was associated with statistically significant protection against hospitalization (adjusted hazard ratio (aHR) = 0.49; 95% CI, 0.46 to 0.53), regardless of age, and receipt of 2 or 3 or more vaccine doses. Limitations include the inability to assess adherence to NMV-r, that test positivity dates may not reflect actual onset of

symptoms, and that individuals who were asymptomatic may have been included in the comparison group, which could potentially bias estimates to the null.[9]

The seventh study[12] (Pandit et al., 2023) assessed time to viral and symptom clearance, as well as COVID-19 rebound among patients with COVID-19 who received NMV-r (n = 127) compared to no treatment (n = 43).[12] The risk of bias from this study was assessed as critical (Table 4). Both groups were provided with 12 rapid antigen tests and instructed to follow a regular testing schedule for 16 days and complete symptom surveys. At baseline, patients who were white were statistically significantly more likely to receive NMV-r compared to controls. The incidence of viral rebound was 14.2% in the NMV-r group and 9.3% in the no treatment group. Symptom rebound incidence was higher in the NMV-r group (18.9%) than in the control group (7.0%). There was no difference in the incidence of viral rebound (14.2% versus 9.3%; P = 0.41), time to viral clearance (mean = 7.1 days versus 7 days; P = 0.85), and time from symptom onset to first negative antigen test (mean = 6.8 days versus 6.1 days; P = 0.80) in the NMV-r group compared to the no treatment group. Limitations include the predominantly white population in the NMV-r group, the smaller control group, and the exclusion of 31% of participants who initially consented due to missing data.[12]

Discussion

Evidence at a moderate risk of bias suggests that in most studies, NMV-r compared to no treatment is associated with a reduced risk of ED visits, hospitalization, and mortality in adults with mild to moderate SARS-CoV-2 infection who were not hospitalized during the Omicron BA.2, BA2.12.1, BA.4, and BA.5 subvariant period. Among individuals with 0 to 1 comorbidity, 2 studies found no significant benefit in the receipt of NMV-r compared to no treatment in reducing the risk of hospitalization or mortality. Among individuals aged 50 years to 64 years, 1 study found no significant difference in the receipt of NMV-r compared to no treatment.

Key Point
Observational study findings suggest that nirmatrelvir-ritonavir reduces the risk of ED visits, hospitalization, and death in outpatient adults with mild to moderate infection, regardless of age or vaccination status.

Limitations across studies include residual confounding, unmeasured adherence to antiviral therapy, exclusion of rapid antigen tests, and inconsistent symptom reporting, which may impact the generalizability of these findings.

NMV-r Versus No NMV-r

Four observational studies compared the outcomes of individuals who received NMV-r to those who did not receive NMV-r for mild to moderate SARS-CoV-2 infection. Two of the studies were conducted in Canada[18,19] and 2 were conducted in the US.[16,17] All 4 studies were assessed as having a moderate risk of bias (Table 6).

All studies used data from EHRs and could not rule out the use of other antiviral or monoclonal therapies in the control group. However, some studies noted that the proportion of patients in the control groups who received these therapies was likely very small due to accessibility of other treatments at the time. All the studies attempted to create balanced intervention and control groups by using propensity score and inverse probability weighting methods. Outcomes reported across studies include COVID-19–related hospitalizations, any cause hospitalizations, and composite outcomes of hospitalizations, mortality, and ED visits (Table 7).

Limitations
The studies excluded rapid antigen tests, there are inconsistencies in symptom reporting, therapy adherence is not measured, and there are uncontrolled confounders. This may affect the generalizability of the findings.

Summary
Four observational studies compared nirmatrelvir-ritonavir to no nirmatrelvir-ritonavir. A meta-analysis was not possible because of the differences across the studies.

Risk of Bias
All 4 studies are at moderate risk of bias.

Table 6

Risk Of Bias Assessment — Strengths and Limitations of Studies Comparing NMV-r to No NMV-r

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Ganatra 2023 [17]	−	+	+	+	+	+	+	−	Matched cohorts, objective endpoints, results robust to sensitivity analyses	Potential confounders not captured in EHR, all-cause mortality or hospitalization may have occurred due to non-COVID-19–related illness

Author Year	Risk of bias	Strengths	Limitations
Kabore 2023 [19]	D1 (−) D2 (+) D3 (+) D4 (+) D5 (+) D6 (+) D7 (+) Overall (−)	Matched cohorts, objective endpoints, results robust to sensitivity analyses	Limited information on concomitant use of other medications, specific criteria for access to NMV-r may limit generalizability
Lewnard 2023 [16]	D1 (−) D2 (+) D3 (+) D4 (+) D5 (+) D6 (+) D7 (+) Overall (−)	Matched cohorts, objective endpoints	Unable to capture previous infections or treatment adherence, low risk of severe disease in highly vaccinated population
Schwartz 2023 [18]	D1 (−) D2 (+) D3 (+) D4 (+) D5 (+) D6 (+) D7 (+) Overall (−)	Matched cohorts, reduced immortal time bias by inputting theoretical dispensing dates for controls	Unable to capture rapid antigen tests, assess adherence, or test positivity dates

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results

Judgement

(+) Low (−) Moderate (x) High (!) Critical (?) Unclear

EHR = electronic health record; NMV-r = nirmatrelvir-ritonavir.

Table 7

Reported Effect Measures by Subgroups in Studies Comparing NMV-r to No NMV-r

First author, year	Overall outcomes	< 70 years	≥ 70 years	Vaccinated	Unvaccinated	Comorbidities	Without comorbidities
Mortality							
Schwartz, 2023[18]	OR = 0.49 (95% CI, 0.40 to 0.60)[a]	NR	NR	NR	NR	NR	NR
COVID-19–related hospitalization							
Kabore, 2023[19]	RR = 0.31 (95% CI, 0.28 to 0.36)[a]	RR = 1.20 (95% CI, 0.87 to 1.65)	RR = 0.75 (95% CI, 0.63 to 0.88)[a]	RR = 0.93 (95% CI, 0.78 to 1.08)	No or incomplete vaccination RR = 0.04 (95% CI, 0.03 to 0.06)[a]	NR	NR
Composite outcome of Covid-19–related hospitalization and mortality							
Lewnard, 2022[16]	aHR = 79.6% (95% CI, 33.9 to 93.8)[a]	NR	NR	aHR = 83.1% (95% CI, 30.4 to95.9)[a]	NR	NR	NR
Schwartz, 2023[18]	OR = 0.56 (95% CI, 0.47 to 0.67)[a]	OR = 0.34 (95% CI, 0.15 to 0.79)[a]	OR = 0.55 (95% CI, 0.45 to 0.66)[a]	1-2 doses OR = 0.25 (95% CI, 0.12 to 0.50)[a] 3+ doses OR = 0.62 (95% CI, 0.51 to 0.75)[a]	OR = 0.44 (95% CI, 0.23 to 0.84)[a]	3 + = 0.54 (95% CI, 0.39 to 0.73) < 3 = 0.57 (95% CI, 0.46 to 0.71)[a]	NR
Composite outcome of all-cause hospitalization, ED visits, and mortality							
Ganatra, 2023[17]	OR = 0.5 (95% CI, 0.39 to 0.67)[a]	NR	NR	NR	NR	NR	NR

aHR = adjusted hazard ratio; CI = confidence interval; ED = emergency department; NMV-r = nirmatrelvir-ritonavir; NR = not reported; OR = odds ratio; RR = relative risk.

[a]Statistically significant.

The first study[17] (Ganatra et al., 2023) was a propensity score matched cohort study conducted in the US that used data from the TriNetX network, a database with patient data from 19 countries.[17] The overall risk of bias in this study was assessed to be moderate (Table 6). The study compared the 30-day composite outcome of all-cause ED visits, hospitalization, or mortality in adult patients who received NMV-r (1,130) with matched controls who received no treatment (1,130). The primary composite outcome was observed in 89 patients (7.87%) in the NMV-r cohort compared to 163 patients (14.4%) in the non–NMV-r cohort (OR = 0.5; 95% CI, 0.39 to 0.67), indicating a statistically significant 45% RR reduction. Receipt of NMV-r was associated with a statistically significant reduction in multisystem symptom burden and subsequent complications such as lower respiratory tract infection, cardiac arrhythmia, and diagnostic radiology testing. Study limitations include potential unmeasured confounders not captured in EHRs, including receipt of vaccination. In addition, the outcome of hospitalization or mortality may have occurred due to illness that was not related to COVID-19 (Table 6).[17]

The second study[19] (Kabore et al., 2023) was conducted in Canada and assessed the risk of 30-day COVID-19–related hospitalization in outpatients who received NMV-r (8,402) compared to propensity score-matched controls (8,402) who did not receive any antiviral therapy in Quebec.[19,36] The study was assessed as having a moderate risk of bias (Table 6). Overall, 58% of the cohort were female, 57% were aged 60 and older, 56% did not have a complete primary vaccination series, 51% had 5 or more comorbidities, 18% were severely immunocompromised, and 16% had cancer. After matching, no significant differences were noted across patient demographic or clinical characteristics. Irrespective of vaccination status, NMV-r was associated with a statistically significant 69% RR reduction of hospitalization among infected patients with a high risk of complications (RR = 0.31; 95% CI, 0.28 to 0.36).[19]

In outpatients with a complete primary vaccination course, the time since the last vaccination dose impacted the results.[36] In

outpatients considered high risk who were aged 70 and older, NMV-r was associated with a 25% reduced RR of COVID-19–associated hospitalization, and the effect was stronger in those whose last dose of the vaccination was received more than 6 months before (RR = 0.50; 95% CI, 0.34 to 0.74 and number needed to treat = 10; 95% CI, 7 to 20). The use of NMV-r had no effect on COVID-19–associated hospitalization for outpatients who were completely primary vaccinated and younger than 70 years, regardless of time elapsed since the last dose. In patients who were severely immunocompromised, NMV-r was associated with a 34% reduction of RR of COVID-19–associated hospitalization irrespective of time elapsed since their last dose of the vaccine.[36]

Among patients with an incomplete primary vaccination course, the RR reduction was larger at 96% (RR = 0.04; 95% CI, 0.03 to 0.06); however, NMV-r had no effect in patients younger than 70 with a complete primary vaccination course.[36] Study limitations include the specific eligibility criteria for accessing NMV-r in Quebec, and potential confounders not captured in EHRs, including COVID-19 and comorbidity severity, concomitant use of remdesivir and anti–SARS-CoV-2 monoclonal antibodies, hybrid immunity from prior infections due to discontinuation of systematic PCR tests, obesity, and tobacco use. In addition, the control cohort did not have to meet the eligibility criteria for NMV-r prescription and were limited to only individuals with positive PCR tests, while the treatment group included both outpatients with and without positive reverse transcription PCR tests.[36]

The third study[16] (Lewnard et al., 2023) was a matched-cohort study that assessed 30-day any cause hospitalization or mortality outcomes in individuals with records in the Kaiser Permanente Southern California health system with confirmed COIVD-19 infection who received NMV-r (n = 7,274) compared to those who did not receive NMV-r (n = 126,152).[16] The risk of bias overall was assessed as moderate (Table 6). The overall estimated effectiveness reported as (1 – hazard ratio) of NMV-r in preventing hospital admission or death within 30 days of a positive test was 53.6% (95% CI, 6.6 to 77.0). However, when NMV-r was administered within 5 days of

symptom onset, the estimated effectiveness increased to 79.6% (95% CI, 33.9 to 93.8). In the subgroup of patients tested within 5 days of symptom onset and who received treatment on the day of their test, the estimated effectiveness of NMV-r was 89.6% (95% CI, 50.2 to 97.8). Limitations include potential misclassification of hybrid immunity due to previously undiagnosed SARS-CoV-2 infections, unmeasured confounding, inability to assess treatment adherence, and the use of matching to accommodate interactions, which resulted in wide CIs. Furthermore, the low risk of severe disease within the highly vaccinated study population further limited the precision of estimates and the ability to explore effect modification.[16]

The fourth study[18] (Schwartz et al., 2023) was conducted in Ontario, Canada, and assessed 30-day COVID-19–related hospitalization and all-cause mortality in outpatients who received NMV-r (8,876) compared to those who did not receive any antiviral therapy (168,669) for confirmed SARS-CoV-2 infection.[18] Overall, the study was assessed as having a moderate risk of bias (Table 6). Before applying propensity score-derived inverse probability of treatment weighting, major between-group differences were observed across most variables. Recipients of NMV-r were older (72% were ≥ 70 years), more likely to have 3 or more vaccines doses, and had more comorbidities. After weighing, no clinically important differences were observed between covariates (SMD ≤ 0.03). The incidence of hospitalization or death was statistically significantly lower in the NMV-r treatment group compared to the untreated group (2.1% versus 3.7%). The weighted OR was 0.56 (95% CI, 0.47 to 0.67). For death alone, the weighted OR was 0.49 (95% CI, 0.39 to 0.62). These findings remained consistent across different age groups, potential drug-drug interactions, vaccination status, and comorbidities. The number needed to treat to prevent 1 case of severe COVID-19 was 62 (95% CI, 43 to 80), with some variation observed across different subgroups. Limitations include the inability to assess rapid antigen tests and treatment adherence not captured in EHRs. Additionally, the use of NMV-r was limited to patients at higher risk of the outcome, which may introduce significant confounding.[18]

Discussion

Moderate-quality evidence suggests that NMV-r compared to no NMV-r is associated with a statistically significant reduction in the risk of hospitalizations and the composite of hospitalization and mortality among adult outpatients with mild to moderate SARS-CoV-2 infection who are considered at risk. However, 1 Canadian study at moderate risk of bias found that the receipt of NMV-r had no significant effect in reducing the risk of COVID-19–related hospitalization in fully vaccinated individuals aged 70 and younger.

Key Point
The observational study findings suggest that nirmatrelvir–ritonavir reduces the risk of hospitalizations, and hospitalizations or death in outpatient adults with mild to moderate infection.

The use of NMV-r may also reduce the risk of severe outcomes and complications such as lower respiratory tract infection and cardiac arrhythmia. NMV-r may be more effective if administered as soon as possible after symptom onset. However, unmeasured confounders stemming from unaccounted differences in treated versus nontreated patients, concomitant use of other antivirals, and hybrid immunity from previous SARS-CoV-2 infections may impact the applicability of these findings.

Limitations
The studies have limited information on hybrid immunity and the use of other antivirals, and there are uncontrolled confounders. This may affect the applicability of the findings.

NMV-r Versus Molnupiravir

Ten studies compared NMV-r to molnupiravir.[15,20-28] Seven studies were conducted in Italy,[20-23,25,26,28] 2 were conducted in the US,[15,27] and 1 was conducted in Japan.[24] Seven studies were assessed as having a moderate risk of bias,[15,21,22,25-28] while the remaining 3 studies were assessed as having a high risk of bias[20,23,24] (Table 8). Three studies reported on the composite outcome of hospitalization or mortality, 6 studies reported on COVID-19–associated hospitalization and/or mortality, 4 studies reported on any cause hospitalization, and 3 studies reported on mortality. The remaining studies each reported outcomes on tolerability and safety, viral load decrease in nasopharyngeal swabs, and time to negativization (i.e., seronegative status) (Table 9).

Summary
Ten observational studies compared nirmatrelvir-ritonavir to molnupiravir.

Risk of Bias
Seven studies are at moderate risk of bias and 3 studies are at high risk of bias.

Table 8

Risk Of Bias Assessment — Strengths and Limitations of Studies Comparing NMV-r to Molnupiravir

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Bajema 2022 [15]	−	+	+	+	+	+	+	−	Matched groups, incorporated Veteran Affairs EHR data	Unable to ascertain symptom onset
Cegolon 2023 [28]	−	+	+	−	+	+	−	−	Objective endpoints, results adjusted for confounders	Potential underestimation of negative tests, baseline differences in age, comorbidities, and time to start of treatment
Cowman 2023 [27]	−	−	+	+	+	−	+	−	Objective endpoints, adjusted results for potential confounders	Inability to assess adherence, lack of untreated control group, incomplete information on vaccination status
Del-Borgo 2023 [23]	x	+	+	?	+	?	−	x	Objective endpoints (hospitalization, death)	Subjective self-reporting (vital signs, symptoms), potential confounding
Gentile 2022 [21]	−	+	−	+	−	+	+	−	Outcomes in vaccinated older adults during the omicron surge	Lack of untreated control group, absence of systematic follow-up to assess viral clearance
Manciulli 2023 [25]	−	+	+	+	+	+	+	−	Matched groups, objective outcomes	Fully vaccinated patients, NMV-r not available for first half of study period
Mazzitelli 2023 [264]	−	+	+	?	+	+	+	−	Objective endpoints, assessed adherence by asking patients to return unused medication	Self-reporting of adverse events, lack of untreated control group

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Mazzotta 2022 [20]	x	+	+	?	+	+	+	x	Assessed viral load decrease as objective surrogate of drug activity in context of high vaccination	Significant differences in baseline risk factors for progression to severe COVID-19
Mutoh 2023 [24]	x	+	+	+	+	+	+	x	Objective endpoints (hospitalization or death)	Retrospective single centre study, self-reported outcomes
Tiseo 2022 [22]	-	+	+	+	-	+	-	-	Objective endpoints (hospitalization or death)	Possibility of allocation bias

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results.

Judgement

+ Low - Moderate x High ! Critical ? Unclear

EHR = electronic health record; NMV-r = nirmatrelvir-ritonavir.

Table 9

Reported Effect Measures by Subgroups in Studies Comparing NMV-r to Molnupiravir

First author, year	Overall outcomes	< 60 years	≥ 60 years	Vaccinated	Unvaccinated	Comorbidities	Without comorbidities
Mortality							
Bajema, 2022[15]	HR = 1.08 (95% CI, 0.62 to 1.89)	NR	NR	NR	NR	NR	NR
Manciulli, 2023[25]	RR = 1.70 (95% CI, 0.03 to 85.3)	NR	NR	NR	NR	NR	NR
Mutoh, 2023[24]	RR = 9.33 (95% CI, 0.86 to 101.2)	NR	NR	NR	NR	NR	NR
All-cause hospitalization							
Cowman, 2023[27]	OR = 1.16 (95% CI, 0.4 to 3.3)	NR	NR	NR	NR	NR	NR

First author, year	Overall outcomes	< 60 years	≥ 60 years	Vaccinated	Unvaccinated	Comorbidities	Without comorbidities
Bajema, 2022[15]	HR = 0.80 (95% CI, 0.56 to 1.16) HR = 1.07 (95% CI, 0.83 to 1.37)	NR	NR	NR	NR	NR	NR
Manciulli, 2023[25]	RR = 1.28 (95% CI, 0.29 to 5.62)	NR	NR	NR	NR	NR	NR
COVID-19–related hospitalization							
Cowman, 2023[27]	aOR = 2.61 (95% CI, 0.34 to 20.13)	NR	NR	NR	NR	NR	NR
Cegolon, 2023[28]	OR = 5.80 (95% CI, 0.28 to 122.16)	NR	NR	NR	NR	NR	NR
Gentile, 2022[21]	RR = 1.82 (95% CI, 0.92 to 4.23)	NR	NR	NR	NR	NR	NR
Mutoh, 2023[24]	RR = 1.32 (95% CI, 0.26 to 6.79)	NR	NR	OR = 0.70 (95% CI, 0.39 to 1.27)	NR	NR	NR
Composite outcome of hospitalization and mortality							
Mazzotta, 2023[20]	OR = 6.87 (95% CI, 0.33 to 144.97)	NR	NR	NR	NR	NR	NR
Tiseo, 2022[22]	RR = 1.03 (95% CI, 0.99, 1.07)	HR = 1.46 (95% CI, 0.21 to 9.92)	NR	NR	NR	NR	NR
Viral and symptom rebound							
Del-Borgo, 2022[23]	OR = 0.56 (95% CI, 0.37 to 0.8)[a]	NR	NR	NR	NR	NR	NR
Adverse events							
Mazzitelli, 2023[26]	RR = 1.29 (95% CI, 1.21 to 1.38)	OR = 0.41 (95% CI, 0.27 to 0.65)[a]	NR	OR = 0.69 (95% CI, 0.29 to 1.68)	NR	OR = 1.14 (95% CI, 0.90 to 1.43)	NR

aOR = adjusted odds ratio; CI = confidence interval; HR = hazard ratio; NMV-r = nirmatrelvir-ritonavir; NR = not reported; OR = odds ratio; RR = relative risk

Note: Only studies that reported numerical results are shown in this table.

[a]Statistically significant.

The first study[15] (Bajema et al., 2022) was conducted in the US and assessed the effectiveness of NMV-r against molnupiravir in reducing the risk of 30-day all-cause hospitalization or death in patients considered at risk with confirmed COVID-19 and records in the Veterans Health Administration database.[15] The study was assessed as having a moderate risk of bias (Table 8). Records of veterans who tested positive for COVID-19 were matched depending on the receipt of antivirals, NMV-r or molnupiravir (769 in each arm).[37] Across the matched groups, 90% of participants were male, the median age was 68 years, and most were white (72% to 75%), with a median of 4 risk factors associated with severe COVID-19. Overall, 26% of patients were unvaccinated. Compared to participants who received molnupiravir, there was a statistically significant reduction in absolute risk of death among those who received NMV-r (rate difference = −7.89 events per 1,000 persons; 95% CI, −15.00 to −0.61) although the RR was not statistically significant (RR = 0.14; 95% CI, 0.02 to 1.16). No significant differences in 30-day hospitalization or 80-day risk of hospitalization or death were observed among participants who received NMV-r versus molnupiravir. Limitations include the inability to assess true symptom onset and prior infections, which may provide background immunity and impact the effectiveness of antiviral treatment. In addition, patients were predominantly male (90%) and the capture of outpatient outcomes, including hospitalizations and COVID-19 treatments, may be incomplete.[15]

The second study,[28] (Cegolon et al., 2023) was conducted in Italy and assessed the effectiveness of NMV-r (n = 102), and molnupiravir (n = 116), to standard of care (n = 111) on COVID-19–associated hospitalization, mortality, and time to negative swab test.[28] The study was assessed as having a moderate risk of bias (Table 8). The rate of COVID-19–associated hospitalization was 2.9% in patients who received NMV-r, and no patient who received molnupiravir was hospitalized (0%). The median time until first negative swab test was 7 days for those who received NMV-r compared to 8 days for those who received molnupiravir. Limitations include the potential underestimation of negative test rates, the small number of participants and statistically significant baseline differences in

age, immunosuppression, time to start of treatment, and use of the Charlson Comorbidity Index, though these factors were adjusted for in multivariable analyses.

The third study[27] (Cowman et al., 2023) was conducted in the US and compared the odds of 30-day all-cause hospitalization and COVID-19–related hospitalization among outpatients who received NMV-r (2,998) and molnupiravir (209) for mild to moderate SARS-CoV-2 infection.[27] The overall risk of bias in this study was assessed as moderate (Table 8). At baseline, patients who received NMV-r were statistically significantly more likely to be younger, female, and have lower rates of at-risk comorbidities, including cancer, chronic kidney disease, and heart conditions compared to those who received molnupiravir. There was no statistically significant difference in the unadjusted OR of 30-day all-cause hospitalization or COVID-19–related hospitalization between those who received NMV-r and those who received molnupiravir. After adjusting for age and number of high-risk conditions, no statistically significant difference in the odds of hospitalization was observed between patients who received NMV-r and those who received molnupiravir (OR = 1.16; 95% CI, 0.4 to 3.3; P = 0.79). Limitations include the inability to assess adherence, the lack of an untreated control group, and potential incomplete information on participant vaccination status.[27]

The fourth study[23] (Del-Borgo et al., 2023) was conducted in Italy and compared the effectiveness and tolerability of NMV-r, molnupiravir, and remdesivir in adults with COVID-19 at high risk of progression to severe disease.[23] The study was assessed as having a serious risk of bias (Table 8). Eligible patients were treated for early COVID-19 at a clinic and were assessed for clinical conditions and polypharmacy at baseline before the oral antiviral was prescribed. Thirty days after the start of therapy, telephone follow-up was performed to evaluate the persistence of symptoms (e.g., cough, dyspnea, fever), the evolution of illness (e.g., pneumonia, hospitalization, death), time to negativization, and AEs. Patients were also encouraged to document symptoms, AEs, and vital signs in a diary for 30 days. In the 10-month observation period,

389 patients received NMV-r and 9,499 received molnupiravir. At baseline, the clinical and demographic characteristics of patients in each group were statistically significantly different, including age, vaccination status, immunodeficiency, and cardiovascular and neurological disease. In the NMV-r group, 93% of patients were fully vaccinated compared to 95% in the molnupiravir group. Patients with neurological and cardiovascular diseases were more likely to receive molnupiravir than NMV-r. Subgroup analysis of patients who were immunocompromised (those with HMs, solid tumours, HIV infection, a transplant, autoimmune diseases, and any other immunosuppressant diseases) was conducted.[23]

Clinical progression, progression to pneumonia, and acute respiratory distress syndrome or non–COVID-19 death were low and similar for both antivirals (progression with NMV-r was 1.3% versus 2.8% for molnupiravir).[23] All 3 COVID-19–related deaths occurred in the molnupiravir group. In the primary analysis, NMV-r was associated with a statistically significantly shorter time to negativization compared to molnupiravir (median = 8 days versus 10 days; P< 0.001) and was also statistically significantly associated with early negativization in the sub analysis of the immunocompromised group. No SAEs were reported in either group; however, the NMV-r group showed a higher incidence of AEs (54%) than the molnupiravir group (22.5%). Most of the reported AEs in the NMV-r group were dysgeusia and diarrhea. WDAEs were reported in 6 patients in the NMV-r group and 5 in the molnupiravir group. Potential limitations of this study include its retrospective nature, the absence of an untreated control group, statistically significant differences in age and comorbidities across groups at baseline, and self-reported results (Table 9).[23]

The fifth study[21] (Gentile et al., 2022) included all patients who were referred to the Unit of Infectious Diseases at the University of Naples Federico II in the Campania region of Italy.[21] Overall, the study was assessed as having a moderate risk of bias (Table 8). The study compared COVID-19–related hospitalization, all-cause hospitalization, mortality, and safety outcomes among 257 patients who received NMV-r (43.2%) compared to molnupiravir (56.8%)

for confirmed SARS-CoV-2 infection. Patients in the molnupiravir group were older, had a lower BMI, and had a higher rate of chronic heart disease compared to those treated with NMV-r. One hospitalization occurred in the NMV-r group (0.9%), compared to 3 in the molnupiravir group (2.1%). No deaths occurred in the NMV-r group, compared to 1 in the molnupiravir group. All hospitalizations were related to COVID-19 symptoms. The median time to test negativity was 8 days in the NMV-r group compared to 10 days in the molnupiravir group ($P < 0.01$). Overall, 37 AEs were observed (mainly dysgeusia, diarrhea, and nausea) in 31 individuals. A higher proportion of patients who received NMV-r reported AEs when compared to those who received molnupiravir (16.2% vs. 8.9%); however, this difference was not statistically significant. Patients who received NMV-r were statistically significantly more likely to report dysgeusia than those who received molnupiravir (9.0% versus 2.7%; $P < 0.05$). Only 2 patients (0.8%) treated with molnupiravir discontinued treatment due to AEs (1 each due to seizure and dizziness). Study limitations include the absence of an untreated control group and baseline differences between the 2 groups.[21]

The sixth study[25] (Manciulli et al., 2023) was conducted in Italy and assessed 28-day COVID-19–related hospitalization or death, and drug tolerability outcomes of patients with COVID-19 considered high risk and treated with NMV-r (120 patients; 15.4%) or molnupiravir (205 patients; 26.3%), as well as sotrovimab and remdesivir.[25] The risk of bias in this study was assessed as moderate (Table 8). Overall, the median age was 69.9 years, 50.4% were male, 36% were immunocompromised, 52% had chronic heart disease, and 84% were fully vaccinated. The group who received NMV-r had the highest percentage of vaccinated people (97%) and the group who received molnupiravir had the highest rate of obese people (30%). No deaths occurred in the NMV-r and molnupiravir groups. Hospitalization occurred in 2.5% of patients in the NMV-r group and 1.9% in the molnupiravir group. In the propensity score-derived inverse probability of treatment weight-adjusted analysis, no statistically significant differences in COVID-19–related hospitalization or death though day 28 were observed between NMV-r or molnupiravir and

the remdesivir reference group. Drug intolerance was reported by 5% of patients in the molnupiravir group (10 out of 205) and 3% in the NMV-r group (6 out of 120). Discontinuation due to intolerance occurred only in the molnupiravir group (5 patients; 2.5%). Limitations include that most patients were fully vaccinated and NMV-r was not available in Italy in the first half of the study period.[25]

The seventh study[26] (Mazzitelli et al., 2023) included all patients who were consecutively referred to the outpatient clinic for early treatment of COVID-19 at the Infectious Diseases Unit of the University Hospital of Padua in Italy.[26] Overall, the study was assessed as having a moderate risk of bias (Table 8). The study retrospectively assessed the tolerability and safety of NMV-r compared to molnupiravir. Out of 909 patients, molnupiravir was prescribed to 407 patients (44.8%), while NMV-r was prescribed to 502 patients (55.2%). Overall, 124 out of 909 patients (13.6%) experienced AEs following the intake of the antivirals. The most reported side effects were dysgeusia (7.4%), bloating (2.3%), diarrhea (2.1%), and nausea and/or vomiting (2%). Three patients (0.3%) reported a severe hypersensitivity reaction (2 treated with molnupiravir and 1 treated with NMV-r). The proportion of patients who experienced an AE was statistically significantly higher in the NMV-r group compared to the molnupiravir group (96 out of 502; 19.1% versus 28 out of 407; 6.9%; $P < 0.05$). The prevalence of dysgeusia and diarrhea was also statistically significantly higher in the group receiving NMV-r than in the molnupiravir group. In patients reporting AEs, no drug interactions were detected between chronic comedication intake and the antiviral drugs described. Overall, 27 patients (3%) reported access to the ED, 4 patients (0.3%) were hospitalized, and 2 patients (0.2%) died. Study limitations include the subjective assessment of some AEs (self-reported), lack of a control group of patients who received no treatment, and the inability to assess biochemical toxicity to determine the real-life safety profile of the treatments.[26]

The eighth study[20] (Mazzotta et al., 2023 was conducted in Italy and assessed the potential decrease of viral load from day 1 to day 7 in nasopharyngeal swabs, COVID-19–related hospitalization, and

all-cause mortality in adult outpatients who received NMV-r (84 patients), remdesivir (118 patients), molnupiravir (117 patients), or sotrovimab (202 patients) for mild to moderate COVID-19.[20] The study was assessed as having a serious risk of bias (Table 8). Patients were followed through day 30 via telephone visit. Overall, 48% of patients were female, 90% were vaccinated, and the median age was 66 years. Omicron BA.1 and BA.2 variants were detected in 73% and 27% of patients, respectively, and mean baseline viral load was 4.12 (standard deviation = 0.27) log2 cycle threshold (4.16 for BA.1 and 4.01 for BA.2). Considering the reduction of viral load as a marker for in-vivo viral activity, NMV-r was statistically significantly more effective in reducing viral load ($P < 0.0001$) in patients infected with BA.1 Omicron strains when compared to molnupiravir; however, there was no difference in activity between NMV-r compared to molnupiravir for patients infected with the BA.2 strain. COVID-19–related hospitalization or all-cause mortality at 30 days follow-up occurred in 2.3% of patients in the NMV-r group; however, no patient in the molnupiravir group experienced hospitalization or died. Limitations include statistically significant differences in baseline risk factors for progression to severe COVID-19 across study groups, outpatient visits with medical evaluation, and that vital sign recording and laboratory tests were scheduled at baseline (day 1 of treatment) and after 7 days.[20]

The ninth study[24] (Mutoh et al., 2023) compared the effectiveness (COVID-19–related hospitalization or death) and safety of NMV-r and molnupiravir in a real-world community setting during the surge of the Omicron BA.5 subvariants in Japan.[24] The overall risk of bias in this study was assessed as serious (Table 8). There were no significant differences in COVID-19–related hospitalization (2.8% in the molnupiravir group and 3.5% in the NMV-r group; $P = 0.978$) or death (0.4% in the molnupiravir group and 3.5% in the NMV-r group; $P = 0.104$) between the 2 groups. The incidence of AEs was 2.7% in the molnupiravir group and 5.3% in the NMV-r group, and the incidence of treatment discontinuation was 2.7% in the molnupiravir group and 5.3% in the NMV-r group. The real-world effectiveness of molnupiravir and NMV-r was similar among older adults and those at high risk of disease progression. The incidence of hospitalization or death

was low. Regarding the cause of death, 1 patient in the molnupiravir group died of terminal gastric cancer on day 6, and 2 patients in the NMV-r group died of suspected acute cardiac events in their homes after completing treatment without requiring hospitalization (on days 8 and 24). Overall, 274 patients (96.8%) completed treatment. AEs were reported in 6 patients (2.7%) in the molnupiravir group and 3 patients (5.3%) in the NMV-r group (P = 0.264). The AEs reported in the molnupiravir group were general fatigue (2 patients) and nausea, rash, throat pain, and diarrhea (1 patient each). The AEs reported in the NMV-r group were nausea, general fatigue, and exacerbation of preexisting interstitial pneumonia (1 patient each). In addition, 3 patients (1.3%) in the molnupiravir group and 2 patients (3.5%) in the NMV-r group discontinued treatment and were hospitalized. All patients who were hospitalized switched to remdesivir. There were no SAEs reported in either group. Study limitations include being a retrospective single-centre observational study, collection of the 28-day outcome from telephone interviews (subjective), lack of data available on patients with COVID-19 who were not prescribed antivirals, and the likelihood of molnupiravir being prescribed to older patients, those with poor performance status, and those with comorbidities, as NMV-r is contraindicated in individuals with impaired kidney function. This may explain the higher mortality rate noted in other studies with molnupiravir compared to NMV-r, as molnupiravir is more likely to be prescribed to patients with multiple comorbidities and polypharmacy.[24]

The 10th study[22] (Tiseo et al., 2023 was conducted in Italy and aimed to assess the composite outcome of 30-day hospitalization or mortality and safety in adult outpatients who received NMV-r (252 patients), molnupiravir (114 patients), or remdesivir (196 patients) for mild to moderate SARS-CoV-2 infection.[22] Overall, the risk of bias in this study was moderate (Table 8). The composite outcome occurred in 0.8% of patients who received NMV-r compared to 1.8% of those who received molnupiravir. Patients who received NMV-r (41%) were statistically significantly more likely to have a negative nasopharyngeal swab within 10 days from the first positive one when compared to those who received molnupiravir (26%). NMV-r was also

associated with a statistically significantly higher incidence of AEs (49%) compared to molnupiravir (21%); P < 0.001. The most reported AE in the NMV-r group was dysgeusia, reported by 42% of patients, and 2.1% of patients discontinued treatment with NMV-r due to AEs, compared to 3.7% in the molnupiravir group. The incidence of rebound was also higher in the NMV-r group (2.1%) compared to the molnupiravir group (1.8%). Limitations include the possibility of allocation bias and residual confounding among the 3 study groups. At baseline, patients who received NMV-r had higher vaccination rates compared to those who received molnupiravir.[22]

Discussion

Evidence from 8 studies that were assessed as having moderate to serious risk of bias suggests that NMV-r is comparable to molnupiravir in decreasing the risk of hospitalization or mortality in patients with mild to moderate SARS-CoV-2 infection. In 1 study, NMV-r was associated with a significantly shorter time to negativization compared to molnupiravir, although clinical progression, progression to pneumonia, and death were similar in both groups. NMV-r was more effective in reducing viral loads in patients infected with the BA.1 Omicron strain compared to molnupiravir; however, no difference in viral activity was observed between NMV-r and molnupiravir for patients infected with the BA.2 strain.

Five studies reported on AEs. All the studies reported a higher incidence of mild to moderate AEs (dysgeusia and diarrhea) in individuals who received NMV-r compared to molnupiravir. In 3 out of the 5 studies, the incidence of AEs was statistically significantly higher among individuals who received NMV-r compared to those who received molnupiravir. WDAEs were reported in 2 studies. In 1 study, no patient in the NMV-r group discontinued treatment due to AEs, while 5 patients discontinued treatment due to AEs in the molnupiravir group. In the second study, a similar number of patients withdrew due to AEs in both groups (5 versus 6). The generalizability of these findings is limited by potential confounding, small sample size, subjective self-reported outcomes in some studies, and single-centre retrospective study designs.

Key Point
Observational study findings suggest that nirmatrelvir-ritonavir is comparable to molnupiravir in decreasing the risk of hospitalizations or death in outpatient adults with mild to moderate infection.

Key Point
Observational study findings suggest that nirmatrelvir-ritonavir has a higher incidence of mild to moderate AEs compared to molnupiravir. Specifically, dysgeusia (distorted sense of taste) and diarrhea.

Limitations
The studies have small sample sizes, self-reported outcomes, and uncontrolled confounders. This may affect the generalizability of the findings.

NMV-r Versus Remdesivir

Four studies compared NMV-r to remdesivir and were conducted in Italy.[20,22,23,25] Three studies reported on the composite outcome of hospitalization and mortality, 2 studies reported on COVID-19–related hospitalization, 1 study reported on tolerability and time to negativization, and the other study reported on decrease in viral load from nasopharyngeal swabs (Table 11). Two studies were assessed as having a moderate risk of bias and the remaining 2 were assessed as having a high risk of bias (Table 10).

Summary
Four observational studies compared nirmatrelvir-ritonavir to remdesivir.

Risk of Bias
Two studies are at moderate risk of bias, and 2 studies are at high risk of bias.

Table 10

Risk Of Bias Assessment — Strengths and Limitations of Studies Comparing NMV-r to Remdesivir

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Del-Borgo 2023 [23]	x	+	+	?	+	?	−	x	Objective endpoints (hospitalization, death)	Subjective self-reporting (vital signs, symptoms), potential confounding
Manciulli 2023 [25]	−	+	+	+	+	+	+	−	Matched groups, objective outcomes	Fully vaccinated patients, NMV-r not available for first half of study period
Mazzotta 2022 [20]	x	+	+	?	+	+	+	x	Assessed viral load decrease as objective surrogate of drug activity in context of high vaccination	Significant differences in baseline risk factors for progression to severe COVID-19
Tiseo 2022 [22]	−	+	+	+	−	+	−	−	Objective endpoints (hospitalization or death)	Possibility of allocation bias

Domains
D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results.

Judgement
+ Low − Moderate x High ! Critical ? Unclear

NMV-r = nirmatrelvir-ritonavir.

Table 11

Reported Effect Measures by Subgroups in Studies Comparing NMV-r to Remdesivir

First author, year	Overall outcomes	< 60 years	≥ 60 years	Vaccinated	Unvaccinated	Comorbidities	Without comorbidities
Mortality							
Manciulli, 2023[25]	RR = 0.23 (95% CI, 0.01 to 4.87)	NR	NR	NR	NR	NR	NR
All-cause hospitalization							
Manciulli, 2023[25]	RR = 0.51 (95% CI, 0.13 to 1.91)	NR	NR	NR	NR	NR	NR
Composite outcome of Covid-19–related hospitalization and mortality							
Manciulli, 2023[25]	HR = 0.51 (95% CI, 0.11 to 2.28)	NR	NR	NR	NR	NR	NR
Tiseo, 2023[22]	RR = 1.03 (95% CI, 0.99 to 1.07)	NR	NR	NR	NR	NR	NR
Mazzotta, 2023[20]	RR = 6.76 (95% CI, 0.32 to 139.1)	NR	NR	NR	NR	NR	NR
Viral and symptom rebound							
Del-Borgo, 2022[23]	OR = 0.56 (95% CI, 0.37 to 0.85)[a]	NR	NR	NR	NR	NR	NR
Mazzotta, 2023[20]	RR = 1.00 (95% CI, 0.96 to 1.04)	NR	NR	NR	NR	NR	NR

CI = confidence interval; HR = hazard ratio; NMV-r = nirmatrelvir-ritonavir; NR = no statistically significant differences were reported; OR = odds ratio; RR = relative risk.

[a]Statistically significant.

The first study[23] (Del-Borgo et al., 2023) was conducted in Italy and compared the effectiveness and tolerability of NMV-r or remdesivir and molnupiravir in adults with COVID-19 at high risk of progression to severe disease.[23] The study was assessed as having a high risk of bias (Table 10). Eligible patients were treated for early COVID-19 at a clinic and were assessed for clinical conditions and polypharmacy at baseline before the oral antiviral was prescribed. After 30 days

of the start of therapy, telephone follow-up was performed to evaluate the persistence of symptoms (e.g., cough, dyspnea, fever), the evolution of illness (e.g., pneumonia, hospitalization, death), time to negativization, and AEs. Patients were also encouraged to document symptoms, AEs, and vital signs in a diary for 30 days. In the 10-month observation period, 389 patients received NMV-r and 230 received remdesivir. At baseline, the clinical and demographic characteristics of patients in each group were statistically significantly different, including age, vaccination status, immunodeficiency, and cardiovascular and neurological disease. In the NMV-r group, 93% of patients were fully vaccinated, compared to 86% in the remdesivir group. Patients with immunodeficiencies were more likely to receive remdesivir. Subgroup analysis of patents who were immunocompromised (those who had HMs, solid tumours, HIV infection, a transplant, autoimmune diseases, and any other immunosuppressant diseases) was conducted.[23]

Clinical progression, progression to pneumonia, and acute respiratory distress syndrome COVID-19 or non–COVID-19 death were low and similar for both antivirals (progression with NMV-r was 1.3% versus 3% with remdesivir).[23] One COVID-19-related death occurred in the remdesivir group and no deaths occurred in the NMV-r group. In the primary analysis, NMV-r was associated with a statistically significantly shorter time to negativization compared to remdesivir (median of 8 days versus 10 days) and was also statistically significantly associated with early negativization in the subanalysis of the immunocompromised group. No SAEs were reported in the 2 groups; however, the NMV-r group showed the highest incidence of AEs (54%) compared to the remdesivir group (14.8%). Most of the reported AEs in the NMV-r group were dysgeusia and diarrhea. WDAEs were reported in 6 patients in the NMV-r group compared to 2 in the remdesivir group. The potential limitations of this study include its retrospective nature, the absence of an untreated control group, statistically significant differences in age and comorbidities across groups at baseline, and self-reported results (Table 10).[23]

The second study[25] (Manciulli et al., 2023) was also conducted in Italy and assessed 28-day hospitalization or death and drug tolerability outcomes of patients with COVID-19 considered high risk and treated with NMV-r (120 patients), remdesivir (142 patients), and molnupiravir (120 patients).[25] The risk of bias in this study was moderate (Table 10). Overall, the median age of participants was 69.9 years, 50.4% were male, 36% were immunocompromised, 52% had chronic heart disease, and 84% were fully vaccinated. The group who received NMV-r had the highest percentage of vaccinated people (97%) and the group who received remdesivir had the highest percentage of smokers (31%).[25]

Deaths occurred in 2 patients in the remdesivir group (1.4%) and no deaths occurred in the NMV-r group.[25] Hospitalization occurred in 2.5% of patients in the NMV-r group and 4.9% in the remdesivir group. In the propensity score-derived inverse probability of treatment weight-adjusted analysis, no statistically significant differences in COVID-19–related hospitalization or death though day 28 were observed between NMV-r or molnupiravir and the remdesivir reference group. Drug intolerance was reported by 5% of patients in the (6 out of 120) NMV-r group and 4% in the remdesivir group (5 out of 142). Discontinuation due to intolerance did not occur in the NMV-r group, and 3 participants discontinued in the remdesivir groups due to intolerance (2.1%). Limitations include that most patients were fully vaccinated and NMV-r was not available in Italy in the first half of the study period (Table 10).[25]

The third study[20] (Mazzotta et al., 2023) was also conducted in Italy and assessed the potential decrease of viral load from day 1 to day 7 in nasopharyngeal swabs, COVID-19–related hospitalization, and all-cause mortality in adult outpatients receiving NMV-r (84 patients), remdesivir (118 patients), molnupiravir (117 patients), or sotrovimab (202 patients) for mild to moderate COVID-19.[20] The study was assessed as having a serious risk of bias (Table 10). Patients were followed through day 30 via telephone visit. Overall, 48% of patients were female, 90% were vaccinated, and the median age was 66 years. Omicron BA.1 and BA.2 variants were detected

in 73% and 27% of patients, respectively, and mean baseline viral load was 4.12 (standard deviation = 0.27) log2 cycle threshold (4.16 for BA.1 and 4.01 for BA.2). Considering the reduction of viral load as a marker for in-vivo viral activity, NMV-r had a stronger antiviral activity in patients infected with the BA.1 and BA.2 Omicron strains when compared to remdesivir. COVID-19–related hospitalization or all-cause mortality at 30 days follow-up occurred in 2.3% of patients in the NMV-r group; however, no patient in the remdesivir group experienced hospitalization or death. Limitations include statistically significant differences in baseline risk factors for progression to severe COVID-19 across study groups, outpatient visits with medical evaluation, and that vital sign recording and laboratory tests were scheduled at baseline (day 1 of treatment) and after 7 days.[20]

The fourth study[22] (Tiseo et al., 2023 was conducted in Italy and aimed to assess the composite outcome of 30-day hospitalization or mortality and safety in adult outpatients who received NMV-r (252 patients) or 3-day remdesivir (196 patients) or molnupiravir (114 patients) for mild to moderate SARS-CoV-2 infection.[22] Overall, the risk of bias in this study was moderate (Table 10). The composite outcome occurred in 0.8% of patients who received NMV-r compared to 5.3% of those who received remdesivir. Patients who received NMV-r (41%) were statistically significantly more likely to have a negative nasopharyngeal swab within 10 days from the first positive one than those who received remdesivir (20%); $P < 0.001$. Receipt of NMV-r was also associated with a statistically significantly higher incidence of AEs (49%) compared to remdesivir (4.66%); $P < 0.001$. The most reported AE in the NMV-r group was dysgeusia (reported by 42% of patients); 2.1% of patients withdrew due to an AE in the NMV-r group, compared to 0% in the remdesivir group. The incidence of rebound was also higher in the NMV-r group (2.1%) compared to the remdesivir group (0%). Limitations include the possibility of allocation bias and residual confounding among the 3 study groups. At baseline, patients who received remdesivir were older and had more comorbidities compared to patients who received NMV-r, and patients who received NMV-r had higher vaccination rates.[22]

Discussion

Evidence at moderate to high risk of bias suggests that NMV-r is comparable to remdesivir in reducing the risk of the composite of hospitalization and mortality in adult outpatients with SARS-CoV-2 infection who are considered high risk. Receipt of NMV-r was associated with a stronger antiviral activity in individuals infected with the BA.1 and BA.2 Omicron strains.

Three studies reported on AEs . Although no SAEs were reported in the studies, 1 study reported that individuals who received NMV-r were statistically significantly more likely to experience mild to moderate AEs. In another study, 42% of individuals who received NMV-r experienced dysgeusia, and 46% reported AEs, compared to 21% of those who received remdesivir. Study limitations , including subjective self-reporting, baseline differences in study groups, and poor reporting standards, may affect the generalizability of these findings.

NMV-r Versus Standard of Care

One observational study[28] (Cegolon et al., 2023) compared NMV-r to standard of care.[28] This study was conducted in Italy and assessed the effectiveness of NMV-r (102 patients), molnupiravir (116 patients), and sotrovimab (57 patients) to standard of care (111 patients) on COVID-19–related hospitalization, mortality, and time to negative swab test. The study was assessed as having a moderate risk of bias (Table 12).

Key Point
Observational study findings suggest that nirmatrelvir-ritonavir is comparable to remdesivir in decreasing the risk of hospitalizations or death in outpatient adults with infection.

Key Point
Observational study findings suggest that nirmatrelvir-ritonavir has a higher incidence of mild to moderate AEs compared to remdesivir. Specifically, dysgeusia (distorted sense of taste).

Limitations
The studies have self-reported outcomes, poor reporting standards, and differences in patient characteristics at the start of treatment. This may affect the generalizability of the findings.

Summary
One observational study compared nirmatrelvir-ritonavir to standard of care.

Table 12

Risk Of Bias Assessment — Strengths and Limitations of the Study Comparing NMV-r to Standard of Care

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Cegolon 2023 [28]	−	+	+	−	+	+	−	−	Objective endpoints, results adjusted for confounders	Potential underestimation of negative tests, baseline differences in age, comorbidities, and time to start of treatment

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results.

Judgement

+ Low − Moderate x High ! Critical ? Unclear

The rate of COVID-19–related hospitalization was 2.9% in patients who received NMV-r and 7.2% in those who received standard of care.[28] Only 2 COVID-19–related deaths occurred during the study period, and both patients received standard of care. Individuals who received NMV-r were statistically significantly less likely to be hospitalized when compared to those who received standard of care (aOR = 0.16; 95% CI, 0.03 to 0.89). The negativization rate was statistically significantly higher in individuals who received NMV-r compared to standard of care (aHR = 1.68; 95% CI, 1.25 to 2.26).[28]

The median time to first negative test was 7 days for patients who received NMV-r and 11 days for patients who received standard of care.[28] Compared to standard of care, patients who received NMV-r were more likely to receive a negative test during the first 5 to 9 days after COVID-19 diagnosis (number needed to treat is 4). However, receipt of 3 or 4 doses of COVID-19 vaccine was statistically significantly associated with a faster negativization rate. Limitations

Risk of Bias
The study is at moderate risk of bias.

include the potential underestimation of negative test rates, the small number of participants and statistically significant baseline differences in age, immunosuppression, time to start of treatment, and use of the Charlson Comorbidity Index, though these factors were adjusted for in multivariable analyses.[28]

Discussion

Evidence assessed as having a moderate risk of bias suggests that NMV-r is more effective than the standard of care in reducing COVID-19-associated hospitalizations. Receipt of NMV-r was also associated with a higher negativization rate and a shorter time to a first negative test compared to standard of care. Limitations of the study, such as the small sample size and baseline differences, may impact the generalizability of the results.

Key Point
The observational study suggests that nirmatrelvir-ritonavir is more effective at reducing hospitalizations and decreasing the frequency and the time to a negative COVID-19 test when compared to standard of care.

Limitations
The study has a small sample size and there is a difference in patient characteristics at the start of treatment. This may affect the generalizability of the findings.

Studies Assessing Specific Populations Within This Literature

Older Adults

Two observational studies assessed the efficacy and safety of NMV-r and molnupiravir in treating COVID-19 among older adults.[29,30] Both studies were assessed as having a moderate risk of bias (Table 13).

Summary
We identified 5 treatment populations for nirmatrelvir-ritonavir: older adults, recipients of a solid organ transplant, and those with inflammatory bowel disease, hematological malignancies, and systemic autoimmune rheumatic disease.

Key Point
For all 5 populations, effectiveness is similar to the general population. Nirmatrelvir-ritonavir reduces hospitalization and death compared to no treatment and is similarly effective compared to other treatments.

Table 13

Risk Of Bias Assessment — Strengths and Limitations in Studies Focused on Older Adults

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Bruno 2022 [29]	−	+	+	+	+	+	+	−	Objective endpoints, addressed underestimation of self-reported side effects	Single centre retrospective design
Gentry 2023 [30]	+	+	+	+	?	+	+	+	Objective endpoints, propensity score matched	Small female population (5%), tolerability and adherence not adequately addressed

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results

Judgement

+ Low − Moderate x High ! Critical ? Unclear

The first study[29] (Bruno et al., 2022) included 168 patients aged 80 years or older.[29] Among them, 21 patients received NMV-r and 147 patients received molnupiravir. Out of a total of 21 hospitalizations reported at 28 days, 9 were attributed to COVID-19 and showed evidence of severe pneumonia leading to acute respiratory failure. The remaining 12 hospitalizations were due to other causes, including 2 for congestive heart failure, 1 for abdominal pain, 1 for a stroke, and 8 due to a decline in general health conditions, such as severe dehydration, senile cachexia, and feeding difficulties. Overall, no significant differences in hospitalizations and deaths were found between treatment with NMV-r and molnupiravir. The study findings revealed that molnupiravir was associated with a statistically significant decrease in composite outcome variables in older females and patients with inadequate vaccination.[29] Moreover, the study reported that hospitalizations and mortality rates at 28 days remained low among the older population as a whole.

The second study[30] (Gentry et al., 2023) involved 813 patients in the NMV-r group, 557 patients in the molnupiravir group, and 1,370 patients in the no antiviral therapy group.[30] These patients were US veterans aged 65 years or older with mild to moderate SARS-CoV-2 infection. A lower proportion of patients who received NMV-r (4.19%) experienced the composite outcome of hospitalization or death at 30 days when compared to patients who received molnupiravir (5.57%); however, this difference was not significant.[30] Additionally, those who received no therapy (10.15%) were statistically significantly more likely to experience the composite event of hospitalization or death at 30 days when compared to those treated with either NMV-r (4.19%) or molnupiravir (5.57%).

There are some limitations to consider. In the first study, only a small proportion of patients (12.5%) received NMV-r, which could potentially affect the generalizability of the findings.[29] In the second study, there were baseline differences between patients who received NMV-r and those who received molnupiravir, particularly in the number of concomitant medications with cautions or contraindications with NMV-r. However, resulting bias may have been somewhat mitigated as comparisons were adjusted for confounding using propensity score matching.[30]

Discussion

These observational studies provide evidence that NMV-r is associated with a lower risk of hospitalization or death in older adults with mild to moderate SARS-CoV-2 infection when compared to molnupiravir or no therapy. However, it is important to consider the limitations of these studies when interpreting the results.

Recipients of a Solid Organ Transplant

Two studies conducted in the US focused on hospitalization and mortality outcomes for recipients of a solid organ transplant who received NMV-r for mild to moderate COVID-19.[31,32] Both studies were assessed as having a moderate risk of bias (Table 14).

Table 14

Risk Of Bias Assessment — Strengths and Limitations of Studies Focused on Recipients of a Solid Organ Transplant

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Radcliff 2022 [32]	−	+	+	+	+	+	+	−	Consistent results with previous studies	Small sample, limited follow up, unable to assess adherence
Hedvat 2022 [31]	−	+	+	+	+	+	+	−	Cohort of SOTR during the Omicron wave	Limited sample size, potential overestimation of morbidity in control group

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results.

Judgement

+ Low − Moderate x High ! Critical ? Unclear

SOTR = recipient of a solid organ transplant.

The first study[32] (Radcliffe et al., 2022) compared NMV-r to molnupiravir, sotrovimab, or no outpatient therapy,[32] while the second compared NMV-r or sotrovimab to no treatment.[31] The first study included only 1 patient who received NMV-r (and this patient did not experience any hospitalization, whether related to COVID-19 or death) compared to 8 (16%) recipients of a solid organ transplant who received molnupiravir, 2 (8%) who received sotrovimab, and 13 (27%) who received no treatment.[32] The receipt of any antiviral was statistically significantly associated with a lower risk of mortality as none of the recipients of a solid organ transplant who received antivirals died, compared to 3 patients who received no treatment.[32]

The second study[31] (Hedvat et al., 2022) compared the effectiveness of NMV-r (28 patients) to no treatment (75 patients) and sotrovimab (51 patients). A total of 14% of patients who received NMV-r were hospitalized for any cause or died by day 30 compared to 33% of

patients who received no treatment (P = 0.009).[31] By day 30, 10.7% of patients in the NMV-r group and 30.7% in the no treatment group experienced COVID-19–related hospitalization or death.

After adjusting for organ transplant type, the receipt of NMV-r (adjusted risk ratio [aRR] = 0.21; 95% CI, 0.06 to 0.71) was significantly associated with lower risk for 30-day any cause hospitalization or death, and COVID-19–related hospitalization or death (aRR = 0.17; 95% CI, 0.04 to 0.67). In a subgroup analysis comparing patients who had completed a primary vaccination series to those who didn't complete a primary series, there was no significant difference in the rate of hospitalization or death among those who received NMV-r compared to those who received no treatment.

These findings should be interpreted with caution due to study limitations. The first study included only 1 patient who received NMV-r, limiting the comparability of NMV-r with other antivirals.[32] The study limitations of the second study include the small number of participants, the possibility of overestimating mortality in the patients who received no treatment, and unobserved confounding.[31]

Discussion

Both studies showed that the receipt of any outpatient antiviral treatment was associated with a reduced risk of hospitalization or death among recipients of a solid organ transplant who had mild to moderate COVID-19. However, it should be noted that in the second study, patients who received NMV-r had a higher risk of hospitalization compared to those who received sotrovimab, though this difference was not significant. The small number of participants in these studies, the possibility of overestimating morbidity and/or mortality outcomes in the no treatment group, and unobserved confounding factors should be considered when interpreting these findings.

Patients With Inflammatory Bowel Disease

One study[33] (Hashash et al., 2023) assessed as having a moderate risk of bias evaluated (Table 15) the risk of 30-day any cause hospitalization, intubation, ICU admission, and mortality among patients with IBD in separate NMV-r (531 patients) and molnupiravir (149 patients) treatment cohorts propensity score-matched 1:1 to no antiviral treatment controls.[33]

Table 15

Risk Of Bias Assessment — Strengths and Limitations of the Study Focused on Individuals With Irritable Bowel Disease

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Hashash 2023 [33]	−	+	+	+	?	+	+	−	Objective endpoints (hospitalization, mortality), propensity scored matched	Inability to assess vaccination impact and timing, immunosuppressive therapies and IBD phenotypes on antiviral efficacy

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results.

Judgement

+ Low − Moderate x High ! Critical ? Unclear

IBD = irritable bowel disease.

Patients who received NMV-r had a statistically significantly reduced risk of hospitalization when compared to controls (aOR = 0.35; 95% CI, 0.1 to 0.74).[33] None of the patients who received NMV-r died or required ICU care or intubation, while 1.8% of patients who were in the no treatment group died. This study demonstrates that treatment with NMV-r is associated with a reduced risk of hospitalization, ICU admission, and mortality in patients with IBD, compared to no

antiviral therapy. The inability of the authors to assess the timing of vaccinations and the receipt of immunosuppressive therapies may impact the generalizability of these findings.[33]

Discussion

Despite the limitations, this study provides valuable insights into the potential benefits of NMV-r in reducing the risk of severe outcomes in patients with IBD. Further enquiry considering additional factors such as vaccination status and immunosuppressive therapies would help provide a more comprehensive understanding of the effectiveness and safety of NMV-r in this population.

Patients With Hematological Malignancies

One study assessed as having a moderate risk of bias (Table 16) evaluated the incidence of COVID-19–related lung failure, deaths, and AEs in patients with HMs with mild to moderate SARS-CoV-2 infection treated with NMV-r (49 patients) compared to those treated with molnupiravir (33 patients).[34]

Table 16

Risk Of Bias Assessment — Strengths and Limitations of the Study Focused on Individuals With Hematological Malignancies

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Minoia 2023 [34]	−	+	−	−	+	−	−	−	Objective endpoints (lung failure, mortality)	Small sample size

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results

Judgement

+ Low − Moderate x High ! Critical ? Unclear

COVID-19–related lung failure occurred in 9 patients who received NMV-r and 10 patients who received molnupiravir.[34] On day 28, COVID-19–related deaths occurred in 2 patients who received NMV-r and 3 who received molnupiravir. No grade 3 or grade 4 AEs were reported, and all patients completed the planned treatment. The findings from this study suggest that NMV-r is comparable to molnupiravir for the treatment of mild to moderate COVID-19 in patients with HMs. However, the lack of an untreated control group and the small number of patients included in this study limits the applicability of its findings.[34]

Discussion

While this study suggests that NMV-r is comparable to molnupiravir in reducing the risk of COVID-19–related lung failure and mortality in patients with HMs, the lack of an untreated control group and the small sample size limit the applicability of the findings.

Adults With Systemic Autoimmune Rheumatic Disease

One study conducted in the US was a retrospective cohort study of adults with SARD with records at Mass General Brigham.[35] The overall risk of bias in this study was assessed as moderate (Table 17).

Table 17

Risk Of Bias Assessment — Strengths and Limitations of the Study Focused on Individuals With Systemic Autoimmune Rheumatic Disease

Author Year	Risk of bias								Strengths	Limitations
	D1	D2	D3	D4	D5	D6	D7	Overall		
Qian 2023 [35]	−	+	+	+	+	+	+	−	Objective endpoints, measured potential confounders (e.g., COVID-19 vaccination status and comorbidities)	Single centre study, high vaccination rates, inability to assess rapid antigen tests, and unmeasured confounding

Domains

D1: Bias due to confounding, **D2:** Bias in selection of participants, **D3:** Bias in classification of interventions, **D4:** Bias due to deviations from intended interventions, **D5:** Bias due to missing data, **D6:** Bias in measurement of outcomes, **D7:** Bias in selection of reported results

Judgement

+ Low − Moderate x High ! Critical ? Unclear

The study compared 30-day hospitalization or mortality and COVID-19 rebound among patients with SARD who received NMV-r (307 patients), no outpatient treatment (278 patients), and monoclonal antibodies (105 patients).[35] Compared to no outpatient treatment, NMV-r was associated with statistically significantly lower odds of hospitalization or mortality (aOR = 0.09; 95%CI, 0.03 to 0.27). The results remained robust in subgroup analyses of age, sex, comorbidity, and vaccination status. Study limitations include potential unmeasured confounders, that the inclusion of only PCR COVID-19 tests in EHRs may have excluded patients who diagnosed themselves at home with rapid antigen tests, and potential undocumented COVID-19 rebound (Table 17).[35]

Discussion

This retrospective cohort study suggests that NMV-r is associated with a statistically significant reduction in the risk of hospitalization or mortality among patients with SARD compared to receiving no outpatient treatment. Despite the study's moderate risk of bias,

the results remained consistent across various subgroups. It is important to consider the limitations, including potential confounding factors, the exclusion of rapid antigen tests from the analysis, and the possibility of undocumented COVID-19 rebound.

Highlighting Studies Conducted in Canada

Summary
Two Canadian studies compared nirmatrelvir-ritonavir to no treatment with nirmatrelvir-ritonavir. Nirmatrelvir-ritonavir reduced hospitalization and death in outpatients with mild to moderate infection who are high risk.

In this section, the focus is on the previously highlighted studies conducted in Ontario and Quebec. As these studies may be the most relevant to the Canadian decision-making context, they are being highlighted here, in addition to considering them alongside the other identified literature in the previous sections. Both studies conducted in different provinces in Canada aimed to assess the effectiveness of NMV-r in reducing COVID-19–associated hospitalizations and mortality in outpatients compared to control groups.

In the first study conducted in Quebec, NMV-r was found to be effective in reducing the risk of hospitalization in outpatients who were severely immunocompromised and outpatients aged 70 years and older who were considered high risk.[19] Notably, among patients with an incomplete primary vaccination course, the RR reduction was even more substantial at 96% (RR = 0.04; 95% CI, 0.03 to 0.06; P < 0.001). However, the use of NMV-r had no effect on COVID-19–associated hospitalization for outpatients younger than 70 years who were completely primary vaccinated, regardless of the time elapsed since the last dose of vaccine. The study included a diverse population with various comorbidities and immunocompromised conditions. Limitations of the study include unmeasured confounders and factors such as concomitant use of other antivirals and hybrid immunity from previous SARS-CoV-2 infections.[19]

The second study conducted in Ontario included a large sample size and assessed 30-day hospitalization and all-cause mortality in recipients of NMV-r compared to those who did not receive any antiviral therapy.[18] The study found a lower incidence of hospitalization or death in the NMV-r group, with consistent findings across different age groups, potential drug-drug interactions,

vaccination statuses, and comorbidities. Before weighting (i.e., propensity score-derived inverse proportion of treatment), there were statistically significant differences observed between the groups across multiple variables. NMV-r recipients tended to be older (72% were ≥ 70 years old), had received 3 or more vaccine doses, and had a higher prevalence of comorbidities. However, after weighting, no clinically important differences were observed between the covariates (SMD ≤ 0.03). However, the study had limitations, including the inability to assess rapid antigen tests, incomplete treatment adherence information, and potential confounding due to the limited use of NMV-r in patients at higher risk. Both studies support the effectiveness of NMV-r in reducing COVID-19–related hospitalizations and mortality among outpatients. However, there are variations in the findings based on factors such as vaccination status and age.[18]

Discussion

Both studies provide evidence supporting the effectiveness of NMV-r in reducing COVID-19–related hospitalizations and mortality among outpatients. These findings underscore the importance of considering patient characteristics, individual risk profiles, and vaccination status when assessing the benefits of NMV-r treatment.

The first study conducted in Quebec highlights the effectiveness of NMV-r in reducing the risk of hospitalization for patients who are severely immunocompromised and outpatients aged 70 years and older who are considered high risk. It also reveals a remarkable reduction in the risk ratio for hospitalization among patients with an incomplete primary vaccination course. However, the study did not find a significant impact of NMV-r on hospitalization rates for outpatients under the age of 70 who were completely primary vaccinated. These results emphasize the potential benefit of NMV-r treatment for specific patient populations with increased vulnerability to severe COVID-19 outcomes.

Key Point
One of the Canadian studies found that although nirmatrelvir–ritonavir is effective in patients who are immunocompromised, no benefit is seen in adults aged 70 and younger who are fully vaccinated.

The second study conducted in Ontario strengthens the evidence for the effectiveness of NMV-r in reducing hospitalization or death across various patient characteristics. The findings consistently

demonstrate lower incidence rates of hospitalization or death in the NMV-r group, irrespective of age, vaccination status, and comorbidities. Importantly, the study applied weighting techniques to address potential confounding factors and observed no clinically important differences between the NMV-r and control groups. However, the study's limitations, including incomplete treatment adherence information and potential confounding due to limited use of NMV-r in patients considered higher risk, should be considered when interpreting the results.

Overall, both studies support the use of NMV-r as an effective treatment option to reduce COVID-19–related hospitalizations and mortality among outpatients. The findings highlight the need for individualized treatment decisions that consider factors such as patient characteristics, risk profiles, and vaccination status. The limitations identified in both studies should be considered, including potential confounding factors and the need for further exploration to provide a more comprehensive understanding of the effectiveness of NMV-r in outpatient settings.

Sex and Gender in This Literature

No studies identified in this review stratified by sex or gender. It remains unknown if there are any differential effects of NMV-r treatment when considering sex or gender.

Vaccination Status and Effectiveness of NMV-r

Summary
Seven observational studies looked at the relationship between vaccination status and the effectiveness of nirmatrelvir–ritonavir.

In total, 7 studies conducted subgroup analyses to examine the effectiveness of NMV-r between individuals who were vaccinated and those who were not.

In the study by Schwartz et al., 2023, conducted in Ontario, the greatest benefits of NMV-r were in individuals who were undervaccinated and unvaccinated.[18] The number needed to treat to prevent 1 all-cause hospital admission or death in individuals who were unvaccinated was 28 with NMV-r compared to 62 overall.[18]

In the study conducted in Quebec, by Kabore et al., 2023, the effect of NMV-r in reducing COVID-19–related hospitalizations or death was modified by vaccination status.[19] In individuals with an incomplete primary vaccination course, the RR was 0.04 (95% CI, 0.03 to 0.06; P < 0.001) compared those not treated with NMV-r. In outpatients with a complete primary vaccination course (at least 2 vaccine doses), treatment with NMV-r did not have a statistically significant effect (RR = 0.93; 95% CI, 0.78 to 1.0; P = 0.321).[19] In those who completed a primary vaccination course, time since last dose and age were further effect modifiers. For those whose last dose was more than 6 months earlier, the relative risk of COVID-19–related hospitalization with NMV-r was 0.62 (95% CI, 0.46 to 0.83; P = 0.01), whereas no statistically significant reduction in risk was found in those whose dose was within the last 6 months.

Another study conducted in the US by Lewnard et al., 2023,[16] found that the estimated effect of NMV-r against all-cause hospitalization or death at 30 days varied depending on an individual's COVID-19 vaccination status. For individuals who had received at least 2 doses of the COVID-19 vaccine, the effectiveness of NMV-r (measured by subtracting the hazard ratios of those who received NMV-r from 1 and multiplying by 100) was 83.1% when administered within 5 days of symptom onset compared to an effectiveness of 79.6% against progression to hospital admission or death due to any cause within 30 days in the treatment group overall. In subgroup analyses of individuals who had received at least 3 doses of the COVID-19 vaccine, the estimated effectiveness against the same endpoint was 92.2% when NMV-r was dispensed within 5 days of symptom onset.[16]

The cohort in the study conducted by Dryden-Peterson et al., 2023, was categorized based on vaccination status (unvaccinated, partially vaccinated, vaccinated, or vaccinated with ≥ 1 booster dose) and recency of the last vaccine dose (< 20 weeks or > 20 weeks, considering the observed decrease in protection against severe disease).[14] NMV-r was associated with increased effectiveness for individuals who were incompletely vaccinated and those who had received their latest dose more than 20 weeks before the study. Following subgroup analysis,

a statistically significant 81% risk reduction (RR = 0.19; 95% CI, 0.08 to 0.49) was shown in individuals who were incompletely vaccinated compared to a statistically significant RR of 0.56 (95% CI, 0.42 to 0.75) for the treated group overall.

In the study by Al-Obaidi et al., 2022,[11] the statistically significant overall difference in proportion of the 30-day hospitalization or mortality composite outcome in NVM-r treated compared to untreated controls (1.2%) was conserved in both the vaccinated (1.0%) and unvaccinated (2.1%) subgroups.[11] The definition of fully vaccinated was not provided.

Shah et al., 2023,[9] completed a retrospective study using the EHR information collected in EPIC, and the aHRs did not differ by vaccination status. The aHR for COVID-19–related hospitalization overall when NMV-r was compared to no NMV-r was 0.49 (95% CI, 0.46 to 0.53) compared to 0.50 (95% CI, 0.45 to 0.55) for those who had 3 or more messenger RNA vaccine doses and 0.50 (95% CI, 0.43 to 0.59) for those who were unvaccinated. There were population differences as older patients who were unvaccinated (≥ 65 years old) benefited more from NMV-r, with an aHR of 0.58 (95% CI, 0.47 to 0.72), than both older vaccinated patients (≥ 3 doses; aOR = 0.51; 95% CI, 0.46 to 0.57) and the unvaccinated general population.

Finally, a study by Aggarwal, 2023,[10] reported subgroup analyses by vaccination status comprising not vaccinated, 1 to 2 doses, and 3 or more doses. Although they found a statistically significant treatment effect for all-cause hospitalization (aOR = 0.45; 95% CI, 0.33 to 0.62; P < 0.0001) and COVID-19–related hospitalization (aOR = 0.40; 95% CI, 0.28 to 0.57; P < 0.0001), there was no difference in effectiveness of NMV-r compared to patients who were untreated across vaccination statuses. Of note, this study was completed during the Omicron BA.4 and BA.5 wave, which may explain the different findings reported by this study compared to the others.

Discussion

While 2 studies found no statistically significant difference in effectiveness across several subgroups of individuals who were vaccinated and those who were not, the remaining 5 studies found NMV-r to be statistically significantly more effective in those who were not vaccinated or incompletely vaccinated, compared to those who were vaccinated.

Key Point
Five studies show nirmatrelvir-ritonavir is more effective in those who are partially vaccinated, undervaccinated, or unvaccinated. Two studies show that it is equally effective across vaccination statuses.

Limitations of the Literature

This systematic review identified several gaps in the literature. First, only 2 RCTs met the inclusion criteria. One RCT compared NMV-r to placebo, while the second compared NMV-r to standard therapy. No RCTs that met the inclusion criteria compared NMV-r to other antivirals, which limits the ability to draw conclusions on the effectiveness of NMV-r compared to other antivirals. Furthermore, the RCTs considered different populations, with 1 RCT including only people who were not vaccinated.

Summary
There are 6 key limitations to the studies included in this review. Notably, none of the studies grouped outcomes by racialized populations, despite their higher likelihood of experiencing poorer clinical outcomes.

Second, more than 90% of the included studies were observational studies, and their risk of bias assessment varied from moderate to critical. Some of the moderate-quality studies attempted to emulate clinical trials by using statistical methods to balance baseline characteristics of the study groups. However, these attempts were often limited by unobserved confounders (e.g., socioeconomic status, access to care) that are not captured in EHRs.

Third, most of the observational studies were unable to assess adherence to antiviral medication, and AEs were often self-reported, which may introduce bias and impact the observed results.

Fourth, some observational studies noted that many participants who received NMV-r and other antivirals did not have a laboratory-confirmed diagnosis (i.e., PCR test) for SARS-CoV-2 infection. This is likely due to the move away from PCR testing to rapid antigen tests. The lack of confirmed diagnosis for SARS-CoV-2 infection means that

in many observational studies, outpatients with COVID-19, particularly those in no treatment control groups, are not captured in EHRs.

Fifth, the potential effect of prior SARS-CoV-2 infections and resulting hybrid immunity on the outcomes of NMV-r treatment have not been adequately explored. This is a complex variable and is further hindered by the underreporting of COVID-19 infections within EHRs due to rapid antigen tests and asymptomatic infections.

Finally, individuals who are racialized are at higher risk of contracting SARS-CoV-2 infection and are more likely to experience poorer clinical outcomes from COVID-19, including hospitalization and mortality, compared to those of other races. However, none of the included studies stratified outcomes by racialized populations, including Indigenous Peoples.

Ongoing Clinical Trials

The search strategy identified 2 nonrandomized ongoing clinical trials, both being conducted in China, that may be relevant to this report. Both clinical trials are listed as "completed" on clinicaltrials.gov but no results are yet available. The first trial was a nonrandomized open-label trial that enrolled 58 individuals aged 12 and older who has SARS-CoV-2 infection confirmed by a positive PCR test within 24 hours of enrolment.[38] The trial aimed to evaluate the efficacy and safety of NMV-r in the treatment of the Omicron variant of COVID-19. Trial outcomes included hospitalization, AEs, and negativization (an important milestone in the management of viral infections, as it indicates that the body's immune response or medical intervention has effectively controlled or eliminated the virus).[38]

The second trial was a prospective, nonrandomized open-label trial that enrolled 18 adults with nonsevere SARS-CoV-2 infection who were undergoing regular hemodialysis 2 to 3 times per week within the past 1 month.[39] The trial aimed to assess the safety of NMV-r in patients with SARS-CoV-2 infection who were receiving hemodialysis.[39]

Summary
There are 2 ongoing nonrandomized clinical trials for nirmatrelvir-ritonavir that may be relevant — 1 assessing safety and efficacy for the omicron variant and the other assessing safety in patients receiving hemodialysis.

Through expert consultation, 1 additional ongoing clinical trial was identified. The trial has been completed, although it is currently unpublished and does not meet the inclusion criteria. The EPIC-SR trial, conducted during both the Delta and Omicron waves, was a phase II/III, double-blind, placebo-controlled study with a 1:1 allocation.[40] It included adult outpatients with COVID-19 who were either fully vaccinated with at least 1 risk factor for severe disease or unvaccinated without risk factors for severe disease. The trial aimed to evaluate the efficacy of NMV-r versus placebo for the treatment of mild to moderate COVID-19 in these patient groups. Notably, dysgeusia and diarrhea occurred more frequently in the NMV-r arms compared to the placebo group. The safety profile of NMV-r remained favourable, with no significant impact observed based on prior COVID-19 vaccination or baseline SARS-CoV-2 serostatus.[40] However, the trial did not demonstrate a meaningful difference in the primary efficacy endpoint of time to sustained symptom alleviation through day 28.[40]

Summary
There is also a trial that has yet to be publicly reported (EPIC-SR) that compares nirmatrelvir-ritonavir to placebo.

Implications of This Literature

This systematic review has several implications. First, while the evidence from the included RCTs found that NMV-r compared to placebo or standard therapy was effective in reducing the risk of hospitalization, mortality, and progression to severe disease, the generalizability of this evidence is limited by 2 factors. One RCT[6] only included patients who were unvaccinated during the Delta wave, which is not representative of the current Canadian population with high vaccination rates and hybrid immunity from previous infections. The other RCT[7] compared NMV-r to an unspecified standard therapy, which limits the ability to appropriately assess the effectiveness of NMV-r.

Second, many of the observational studies noted eligibility requirements for the receipt of NMV-r, including age, immunosuppressed status, and the presence of at least 1 comorbid condition. These requirements are jurisdiction-specific and may limit the generalizability of the results to other settings. Furthermore, eligibility requirements for receipt of NMV-r may introduce bias to

Summary
There are 3 implications to this review: limited generalizability of the RCT results, the high-risk populations included in the observational studies may introduce bias, and the role of vaccination is still emerging.

studies because those who receive the intervention are at a higher risk of the outcomes of disease progression, hospitalization, or mortality.

Third, most studies found that NMV-r compared to no therapy or no NMV-r was associated with reducing the risk of hospitalization or mortality regardless of age or vaccination status; however, 1 study conducted in Quebec arrived at a discordant conclusion.[19,36] The authors found that although NMV-r was beneficial to patients who were severely immunocompromised, it may have no effect on COVID-19–associated hospitalization for patients considered high risk who are aged 70 or younger and have completed their primary vaccination course, regardless of the amount of time that elapsed since their last vaccination.[19,36] This finding may have implications in the context of eligibility for the receipt of NMV-r, particularly in jurisdictions with high vaccination rates.

Conclusions

Evidence from two RCTs assessed as having a low to moderate risk of bias suggests that the receipt of NMV-r compared to placebo or standard treatment significantly reduces the risk of hospitalization, mortality, and progression to severe disease in outpatients with mild to moderate SARS-CoV-2 infection who are considered high risk. However, 1 of these trials only included people who were unvaccinated so the evidence for NMV-r in a general highly vaccinated population, such as Canada, is extremely limited.

The observational studies found no significant difference in the effect of NMV-r compared to other antivirals (i.e., molnupiravir and remdesivir), in reducing the risk of hospitalization and mortality in outpatients with mild to moderate SARS-CoV-2 infection who are considered high risk. In some observational studies, the receipt of NMV-r was associated with a significantly higher risk of mild to moderate AEs when compared to molnupiravir and remdesivir; however, NMV-r was associated with a faster time to a negative test compared to molnupiravir and remdesivir.

The 7 observational studies that focused on specific populations at high risk of progression to severe COVID-19 found that the receipt of NMV-r compared to no treatment was associated with reductions in the risk of hospitalization or mortality, and there was no significant difference in the effect of NMV-r compared to molnupiravir.

In the 7 observational studies that stratified results by vaccination status, 5 studies found that NMV-r was more effective in reducing the risk of hospitalization or mortality in individuals who were unvaccinated, or individuals who had not completed their primary vaccination course when compared to individuals who had completed their primary vaccination course.

Results from the observational studies should be interpreted with caution due to unobserved confounding, study-specific limitations, and the moderate to very low quality of evidence.

Very little is known about how sex and gender or other sociodemographic variables may interact with NMV-r. The lack of diversity within the study populations limits the generalizability of this literature within the Canadian context.

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Clinical Review

Fiona Clement acted as the principal investigator by developing and leading the approach and contributed to drafting and finalizing the report.

Nkiruka Eze contributed to the conceptualization and design of the report, drafted the report, provided data analysis, created figures and tables, interpreted study results, and drafted conclusions and key messages.

Benedicta Asante contributed by screening studies, extracting data, analyzing and interpreting results, and drafting and revising the report.

Research Information Science

Carolyn Spry designed and executed the literature search strategy, monitored search alerts, prepared the search methods section and Appendix 1, managed referencing of the report, and provided final approval to the version of the report submitted for publication.

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Other

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Peter Daley disclosed the following involvements:

- CADTH's Scientific Advice Program: Dalbavancin, 2022
- CADTH's Scientific Advice Program: Molnupiravir, 2021.

No other conflicts of interest were declared.

For more information on CoLab and its work visit **colab.cadth.ca**

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: May 4, 2023 (updated May 8, June 12, June 19)

Alerts: Bi-weekly search updates until June 19, 2023.

Search filters applied: All clinical trials; observational studies (modified)

Limits:

- Language limit: English- and French-language
- Conference abstracts: excluded

Table 18

Syntax guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1 (nirmatrelvir* or Bexovid* or PF07321332 or "PF 07321332" or PF7321332 or PF 7321332 or 7R9A5P7H32).ti,ab,kf,hw,rn,nm. 1774

2 Ritonavir/ 28347

3 (ritonavir* or Norvir* or ABT538 or ABT 538 or A84538 or A 84538 or ABT538 or ABT 538 or ORB102 or ORB 102 or O3J8G9O825 or RTV).ti,ab,kf,hw,rn,nm. 48423

4 2 or 3 48423

5 1 and 4 1400

6 paxlovid*.ti,ab,kf,hw,rn,nm. 708

7 5 or 6 1585

8 7 use medall 556

9 *nirmatrelvir/ 128

10 (nirmatrelvir* or Bexovid* or PF07321332 or "PF 07321332" or PF7321332 or PF 7321332). ti,ab,kf,dq. 1215

11 9 or 10 1221

12 *ritonavir/ 6785

13 (ritonavir* or Norvir* or ABT538 or ABT 538 or A84538 or A 84538 or ABT538 or ABT 538 or ORB102 or ORB 102 or RTV).ti,ab,kf,dq. 22183

14 12 or 13 23148

15 11 and 14 871

16 *nirmatrelvir plus ritonavir/ 317

17 paxlovid*.ti,ab,kf,dq. 676

18 16 or 17 828

19 15 or 18 1232

20 19 use oemezd686

21 20 not (conference abstract or conference review).pt. 627

22 8 or 21 1183

23 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt. 689250

24 (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt. 609798

25 Multicenter Study.pt. 333288

26 Clinical Studies as Topic/ 163678

27 exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/ 3523753
28 Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/ 767629
29 Randomization/ 206068
30 Random Allocation/ 202199
31 Double-Blind Method/ 360078
32 Double Blind Procedure/ 209914
33 Double-Blind Studies/ 342497
34 Single-Blind Method/ 82225
35 Single Blind Procedure/ 51615
36 Single-Blind Studies/ 84290
37 Placebos/ 381587
38 Placebo/ 402378
39 Control Groups/ 112886
40 Control Group/ 112886
41 Cross-Over Studies/ or Crossover Procedure/ 130089
42 (random* or sham or placebo*).ti,ab,hw,kf. 4335047
43 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 627252
44 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 3698
45 (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. 12742845
46 (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf. 8122710
47 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*). ti,ab,hw,kf. 124055
48 (phase adj3 (study or studies or trial*)).ti,ab,hw,kf. 569436
49 ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf. 145974
50 ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. 927189
51 allocated.ti,ab,hw. 191748
52 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. 130862
53 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)). ti,ab,hw,kf. 30189
54 (pragmatic study or pragmatic studies).ti,ab,hw,kf. 1502
55 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. 16295
56 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. 31252

57 trial.ti,kf. 744703
58 or/23-57 18483166
59 exp animals/ 56924197
60 exp animal experimentation/ 3096830
61 exp models animal/ 2406390
62 exp animal experiment/ 3096830
63 nonhuman/ 7466512
64 exp vertebrate/ 55447589
65 [animal.po.] 0
66 or/59-65 59014959
67 exp humans/ 46633963
68 exp human experiment/ 648509
69 [human.po.] 0
70 or/67-69 46636421
71 66 not 70 12379835
72 58 not 71 14914551
73 epidemiologic methods.sh. 31619
74 epidemiologic studies.sh. 9311
75 observational study/ 467180
76 observational studies as topic/ 334699
77 clinical studies as topic/ 163678
78 controlled before-after studies/ 231384
79 historically controlled study/ 241780
80 interrupted time series analysis/ 224750
81 national longitudinal study of adolescent health/ 386
82 cohort studies/ 1218159
83 cohort analysis/ 1356360
84 longitudinal studies/ 337057
85 longitudinal study/ 357435
86 prospective studies/ 1422917
87 prospective study/ 1530094
88 follow-up studies/ 2266347
89 follow up/ 2040441

90 followup studies/ 0
91 retrospective studies/ 2291715
92 retrospective study/ 2572613
93 case-control studies/ 494157
94 exp case control study/ 1635407
95 observational study/ 467180
96 quasi experimental methods/ 0
97 quasi experimental study/ 12279
98 (observational study or validation studies or clinical study).pt. 146606
99 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. 563743
100 cohort*.ti,ab,kf. 2312393
101 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. 1340641
102 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. 438225
103 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf. 836264
104 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf. 1815774
105 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf. 372038
106 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. 1341
107 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf. 583449
108 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. 272797
109 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. 10674
110 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf. 1001190
111 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf. 6831
112 (quasi adj (experiment or experiments or experimental)).ti,ab,kf. 45240
113 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. 4049
114 or/73-113 10721376
115 22 and (72 or 114) 481
116 limit 115 to (english or french) 472

117 remove duplicates from 116 317

Medline results: 176, Embase results: 141

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

Search 1: Completed Studies | nirmatrelvir ritonavir | “COVID-19”

Search 2: Completed Studies | paxlovid | “COVID-19”

Total number of results retrieved: 8 completed trials

Appendix 2: List of Included Studies

Note that this appendix has not been copy-edited.

Table 19

Incuded Studies

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Randomized controlled trials					
Balykova[7] **2022** **Russia** **Y**	Non-hospitalized adults with confirmed mild or moderate symptomatic SARS-CoV-2 infection	NMV-r plus pathogenic and symptomatic therapy Standard therapy	NMV-r: 132 Female 64% Mean 46.6 years % vaccinated: NR Standard of care: 132 Female 62% Mean 46.6 years % vaccinated: NR	Progression to severe disease Frequency of AEs and SAEs	N
Hammond[6] **2022** **UK** **Y** **Also reported in Anderson**[8]	Unvaccinated adults with confirmed symptomatic COVID-19 and symptom onset no more than 5 days before randomization	NMV-r Placebo	NMV-r: 1120 Female 49.5% Median 45 years % vaccinated: None (unvaccinated patients only) Placebo: 1126 Female 48.3% Median 46.5 years % vaccinated: None (unvaccinated patients only)	Hospitalization All-cause mortality Safety Rebound COVID-19	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Observational studies					
Aggarwal[10] **2023** **USA** **N**	Outpatients with positive COVID test, or NMV-r prescription	NMV-r taken orally every 12 hours for 5 days. Patients with moderate renal impairment, NMV-r 150 mg/100 mg every 12 hours for 5 days No treatment	NMV-r: 7168 Female 58.6% Age: 18-44: 45.9% 45-66: 22.1% >65: 32.1% % vaccinated: 1 dose:4.1% 2 doses: 14.8% 3+ doses: 60.7% No treatment: 9361 Female 58.3% Age: 18-44: 63.7% 45-66: 15.4% >65: 20.9% % vaccinated: 1 dose:4.2% 2 doses: 16.4% 3+ doses: 57.6%	Hospitalization Mortality ED Visits	Y

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Al-Obaidi[11] **2023** **USA** **N**	Adult outpatients with NMV-r prescription and no receipt of tixagevimab-cilgavimab injection or BEB infusion, Molnupiravir use prior to the index date, and/or weight greater than 40kg	NMV-r No treatment	NMV-r: 5754 Female 60.1% Mean 58.0 years % vaccinated: 42.0% No treatment: 5754 Female 58.4% Mean 58.0 years % vaccinated: 42.0%	Composite of Hospitalization and Mortality	Y

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Bajema[37] **2022** **USA** **N**	Individuals with a VHA primary care encounter in the 18 months preceding the test-positive date who were alive and not hospitalized on or within 7 days before the test-positive date.	NMV-r Molnupiravir No treatment	NMV-r: 1587 Female 11% Age: 18-49: 17.6% 50-64: 29.2% 65-74: 32.9% >75: 20.3% % vaccinated: 71% Molnupiravir: 769 Female 10% Age: 18-49: 13.1% 50-64: 28.0% 65-74: 35.2% >75: 23.7% % vaccinated: 76.3% No treatment: 1587 Female 11% Age: 18-49: 18.3% 50-64: 27.9% 65-74: 32.3% >75: 21.5% % vaccinated: 69.8%	Hospitalization Mortality	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Bruno[29] **2022** **Italy** **N**	Patients aged ≥80 years with confirmed mild-to-moderate SARS-CoV-2 infection, and at least one comorbidity who received an oral antiviral prescription within 5 days of symptom onset	NMV-r taken orally every 12 hours for a duration of 5 days. Patients with moderate renal impairment, NMV-r 150 mg/100 mg every 12 hours for 5 days Molnupiravir	NMV-r: 21 Female NR Mean NR % vaccinated: NR Molnupiravir: 147 Female NR Mean NR % vaccinated: NR	Hospitalization Mortality Safety	N
Cegolon[28] **2023** **Italy** **N**	Non hospitalized adult outpatients with SARS-CoV-2 infection	NMV-r Standard of care	NMV-r: 102 Female 52.0% Mean 66.2 years % vaccinated: 79.8% Standard of Care: 111 Female 49.6% Mean 70.9 years % vaccinated: 78.3%	Hospitalization Mortality Time to negative swab test	N
Cowman[27] **2023** **USA** **N**	Non-hospitalized adult (≥18 years old) COVID-19 patients	NMV-r Molnupiravir	NMV-r: 2998 Female 67.4% Median 58 years % vaccinated: 81% Molnupiravir: 209 Female 60.3% Median 64 years % vaccinated: 85%	Hospitalization	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Del Borgo[23] **2023** **Italy** **N**	Adult outpatients with positive SARS-CoV-2 test, at least one risk factor for severe COVID-19	NMV-r Remdesivir Molnupiravir	NMV-r: 398 Female 57.1% Median 64 years % vaccinated: 93.8% Remdesivir: 230 Female 49.6% Median 66 years % vaccinated: 86.1% Molnupiravir: 499 Female 51.5% Median 78 years % vaccinated: 94.8%	Persistence of symptoms Evolution of illness Time to negativization Safety	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Dryden-Peterson[14] **2022** **USA** **N**	Adult outpatients aged 50 years or older with COVID-19 and no contraindications for NMV-r	NMV-r No NMV-r	NMV-r: 12541 Female 58% Age: 50-64: 47.0% 65-79: 43.0% >80: 10.0% % vaccinated: 95% No NMV-r: 32010 Female 61% Age: 50-64: 59.0% 65-79: 33.0% >80: 8.0% % vaccinated: 89%	Composite of Hospitalization and Mortality	Y
Epling[13] **2022** **USA** **N**	Adults with relapse of COVID-19 symptoms after treatment with NMV-r, with rebound symptoms without prior antiviral therapy and with acute Omicron infection	NMV-r No NMV-r	NMV-r: 10 Female NR Age: NR % vaccinated: NR No NMV-r: 5 Female NR Age: NR % vaccinated: NR	COVID-19 rebound	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Ganatra[17] **2022** **USA** **N**	Non- hospitalized patients 18 years of age and older who were vaccinated and subsequently developed COVID at least 1 month after vaccination	NMV-r administered within 5 days of diagnosis No NMV-r	NMV-r: 1131 Female 63% Mean age: 57.6 % vaccinated: 100% No NMV-r: 110457 Female 64.3% Mean Age: 49.3 % vaccinated: 100%	Composite Hospitalization, Mortality and ED Visits	N
Gentile[21] **2022** **Italy** **Y**	Patients with SARS-CoV-2 infection not requiring hospitalization due to COVID-19	NMV-r Molnupiravir	NMV-r: 111 Female 57.6% Median 60 years % vaccinated: 98.2% Molnupiravir: 146 Female 47.2% Median 70 years % vaccinated:94.5%	Hospitalization Mortality Safety	N
Gentry[30] **2023** **USA** **N**	Veterans 65 years and older who developed documented SARS-CoV-2 infection between January 1, 2022, and February 6, 2022	NMV-r Molnupiravir	NMV-r: 813 Female 5% Mean age 74.2 % vaccinated: 97.3% Molnupiravir: 557 Female 4.8% Mean age 74.6 % vaccinated: 98.4%	Composite of Hospitalization and Mortality	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Hashash[33] **2023** **USA** **Y**	Patients with IBD with COVID-19 from the TriNetX platform	NMV-r No anti-viral	NMV-r: 532 Female 62% Mean age 55.2 % vaccinated: 17.6% No anti-viral: 29589 Female 60% Mean age 50.3 % vaccinated: 4.3%	Hospitalization Mortality	N
Hedvat[31] **2022** **USA** **N/S**	Adult recipients of a solid organ transplant with asymptomatic, mild, or moderate COVID-19 who had a positive SARS-CoV-2 PCR test conducted within the New York-Presbyterian Hospital health system between December 16, 2021, and January 19, 2022.	NMV-r No treatment	NMV-r: 28 Female 61.7% Mean age 57.6 % vaccinated: 85.8% No treatment: 75 Female 57.3% Mean age 53.3 % vaccinated: 85.3%	Hospitalization Mortality Y	N
Kabore[36] **2023** **Canada** **N**	Outpatients who received at least one prescription of NMV-r in Québec with severe immunosuppression, adults without a complete primary vaccination course with at least one risk factor for severe COVID-19, those with positive COVID test but no receipt of NMV-r	NMV-r No NMV-r	NMV-r: 16601 Female 57.4% Age over 60: 67% % vaccinated: 23.5% No NMV-r: 242337 Female 67.1% Age over 60: 26.4% % vaccinated: 92.5%	Hospitalization	Y

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Lewnard[16] **2023** **USA** **N**	Aged at least 12 years at the time of the index test, received a positive SARS-CoV-2 PCR test result (their index test) taking NMV-r	NMV-r No NMV-r	NMV-r: 7274 Female 57.7% Age over 60: 54.1% % vaccinated: 94.6% No NMV-r: 126152 Female 55.3% Age over 60:24.9% % vaccinated: 86.7%	Composite of Hospitalization and Mortality	Y
Manciulli[25] **2023** **Italy** **N**	Patients treated at the outpatient services between 1 January 2022 and 31 March 2022	NMV-r Remdesivir Molnupiravir	NMV-r: 120 Female 57.5% Median 66.9 % vaccinated: 97.5% Remdesivir: 142 Female 58.5% Median 67.4 % vaccinated: 88% Molnupiravir:205 Female 42.4% Median 68.9 % vaccinated: 88.3%	Composite of Hospitalization and Mortality	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Mazzitelli[26] **2023** **Italy** **N**	Patients prescribed NMV-r or Molnupiravir with symptom onset ≤5 days, high risk of COVID-19 progression, not pregnant and not diagnosed with end stage liver disease	NMV-r Molnupiravir	NMV-r: 502 Female 48.8% Median 68 % vaccinated: 94.4% Molnupiravir:407 Female 51.4% Median 80 % vaccinated: 96.0%	Tolerability Safety	N
Mazzotta[20] **2023** **Italy** **N**	Patients with a confirmed SARS-CoV-2 Omicron (BA.1 or BA.2) diagnosis and mild-to-moderate COVID-19 infection	NMV-r Remdesivir Molnupiravir	NMV-r: 84 Female 57.5% Median 63 % vaccinated: 92.9% Remdesivir: 118 Female 44.1% Median 70 % vaccinated: 85.6% Molnupiravir:117 Female 44.4% Median 68 % vaccinated: 93.1%	Composite of Hospitalization and Mortality Viral load	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Minoia 2023[34] **Italy** **N**	Adults diagnosed with hematologic malignancy and undergoing or with recent (<12 month) anti-tumor therapy (chemotherapy, targeted therapies) or immune suppressive treatment with confirmed SARS-CoV-2 infection, and no contraindication to anti-viral administration	NMV-r Molnupiravir	NMV-r: 49 Female NR Age NR % vaccinated: NR Molnupiravir: 33 Female NR Age NR % vaccinated: NR	Mortality COVID-19-related lung failure Safety	N
Mutoh[24] **2023** **Japan** **N**	Patients with confirmed COVID-19 combined with one or more risk factors for disease progression from June to October 2022	NMV-r Molnupiravir	NMV-r: 57 Female 42.1% Mean Age 68.2 % vaccinated: 80.7% Molnupiravir: 226 Female 45.8% Mean Age 72.6 % vaccinated: 81.3%	Hospitalization Mortality Safety	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Pandit[12] **2022** **USA** **Y**	US resident age ≥18 years with a positive rapid antigen test for SARS-CoV-2 (verified by eMed), and prescribed NMV-r through the telehealth visit regardless of whether they intended to take the medicine	NMV-r No NMV-r	NMV-r: 127 Female 56.7% Age 18-44: 40.2% 45-66: 45.7% >65: 14.2% % vaccinated: 95.3% No NMV-r: 43 Female 62.8% Age 18-44: 51.2% 45-66: 39.5% >65: 9.3% % vaccinated: 95.3%	Time to viral and symptom clearance COVID-19 rebound	N

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Radcliffe[32] **2022** **USA** **N**	Nonhospitalized recipients of a solid organ transplant	NMV-r No treatment Molnupiravir Sotrovimab	NMV-r: 1 Female 100% Mean Age 51 % vaccinated: 100% No treatment: 48 Female 35% Mean Age 51 % vaccinated: 81% Molnupiravir: 49 Female 49% Mean Age 55 % vaccinated: 92%	Hospitalization Mortality	N
Schwartz[18] **2023** **Canada** **N**	Outpatients with positive PCR COVID test, age 17 and older	NMV-r No NMV-r	NMV-r: 8876 Female 59.3% Median Age 77 % vaccinated: 94.7% No NMV-r: 168669 Female 63.4% Median Age 50 % vaccinated: 93.8%	Composite outcome of Hospitalization and Mortality	Y

First Author, Publication Year Country Industry sponsored (Y/N)	Inclusion Criteria	Intervention Comparator/s	Participants Sex Age Vaccinated	Outcomes Stratified by vaccination status (Y/N)	Stratified by vaccination status (Y/N)
Shah[9] **2022** **USA** **N**	Adults with a COVID-19 diagnosis during April 1–August 31, 2022	NMV-r No NMV-r	NMV-r: 198927 Female 61.8% Over 65 years: 37.9% % vaccinated: 84.4% No NMV-r: 500921 Female 63.2% Over 65 years: 26.5% % vaccinated: 71.7%	Hospitalization	Y
Tiseo[22] **2023** **Italy** **Y**	Outpatients with positive COVID test who received one authorized antiviral treatment and did not require supplemental oxygen therapy and had mild-to-moderate COVID-19.	NMV-r Remdesivir Molnupiravir	NMV-r: 252 Female 49.6% Median Age: 65 % vaccinated: 86.9% Remdesivir: 196 Female 42.3% Median Age: 72 % vaccinated: 77% Molnupiravir: 114 Female 45.6% Median Age: 69.5 % vaccinated: 74.6%	Hospitalization Mortality Composite of Hospitalization and Mortality Safety	N

IBD = irritable bowel disease; NMV-r = nirmatrelvir/ritonavir; NR = not reported.