Poster 516

A Systematic Literature Review Evaluating Real-World Use of Nirmatrelvir-Ritonavir for the Prevention of COVID-19-Related Hospitalization and Death

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Breakthroughs that change patients' lives

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Introduction

- Nirmatrelvir-ritonavir (NMV/r) is an oral antiviral used for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset in patients aged ≥12 years at high risk of progression to severe disease, including hospitalization and death
- The Evaluation of Protease Inhibition for COVID-19 In High-Risk Patients (EPIC-HR) trial demonstrated that NMV/r significantly reduced the risk of COVID-19 related hospitalization or death from any cause in unvaccinated patients treated within 5 days of symptom onset by 86% compared to placebo
- Following real-world utilization beginning in late 2021, millions of patients worldwide have been treated with NMV/r and many studies have described outcomes following treatment
- This systematic literature review (SLR) summarized the real-world effectiveness of NMV/r against hospitalization and mortality (separately, and composite), stratified by age, vaccination status, and underlying high-risk condition

Methods

- An SLR was conducted in accordance with the Cochrane Handbook for Systematic Review of Interventions (CHSRI) guidelines[1] and Preferring Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)[2]
- Real-world studies of NMV/r use available in English, with sample size ≥5, and reporting on hospitalization and/or mortality outcomes were identified from Embase and PubMed
- Studies were evaluated for eligibility using population, intervention, comparison, outcome, study design (PICOS) criteria; when summarizing the findings for this presentation, the PICOS criteria were refreshed to include the most recent data (Dec 22, 2021 - Mar 31, 2023) (**Table 1**), supplemented by a review of grey literature from conference proceedings from Dec 1, 2021-Dec 31, 2022
- Dual-independent screening was used at the title, abstract and full-text review stages with third reviewer consensus; data were extracted by a single reviewer with validation by a second reviewer prior to a risk-of-bias assessment
- Differences in treatment effect were reported as adjusted odds ratios (aOR), adjusted hazard ratios (aHR), and adjusted risk ratios (aRR) with corresponding 95% confidence intervals (CIs) as reported in the studies were converted to effectiveness by subtracting the ratio from 1 and multiplying by 100. No statistical analysis was conducted across the studies

Results

Study characteristics (Figure 1)

- Of 66 studies that represented 421,588 patients that received NMV/r, 14 studies reported on effectiveness (i.e., relative risk reduction) for at least one outcome of interest and were included in this SLR
- Of the 14 studies, 8 studies reported that Omicron was predominant during the study; 6 studies reported predominance by Omicron sublineage (BA.1/BA.2 and BA.4/BA.5)
- One study (Lewnard et al.) evaluated NMV/r effectiveness when received within 5 days of symptom onset (in alignment with EPIC-HR and the product label; **Figure 3**)

NMV/r effectiveness against hospitalization

- Studies that measured all-cause hospitalization (n=8) reported effectiveness (percent reduction in odds/risk ratio) ranging from 21% to 89% (NMV/r vs. no NMV/r, **Figure 2A**)
- When considering COVID-19-related hospitalization, all studies (n=3) favored NMV/r treatment with effectiveness of 24%-60%. Treatment benefit of NMV/r was consistent regardless of age, vaccination status, and underlying high-risk conditions

NMV/r effectiveness against mortality

- Five studies reported on effectiveness of NMV/r vs no NMV/r for all-cause mortality, with effectiveness (percent reduction in odds/risk ratio) ranging from 39%-85% (**Figure 2B**)

NMV/r effectiveness against the composite endpoint of hospitalization and mortality

- Seven studies measured effectiveness of NMV/r using a composite endpoint of all-cause hospitalization or mortality; five assessed effectiveness vs no NMV/r with a range of 1%-92% (**Figure 3**)

Conclusions

- Real-world studies show that NMV/r provides effective protection against hospitalization and/or death during the Omicron era, regardless of age, vaccination status, and underlying high-risk conditions
- Limitations of the current analysis include the potential for data duplication due to studies leveraging the same datasets; heterogeneity in cohort selection, study endpoint definitions, and follow-up periods precluded a meta-analysis
- Real-world NMV/r effectiveness should be continually monitored as the natural history of COVID-19 and treatment landscape continue to evolve

Figure 1. Systematic literature review PRISMA diagram

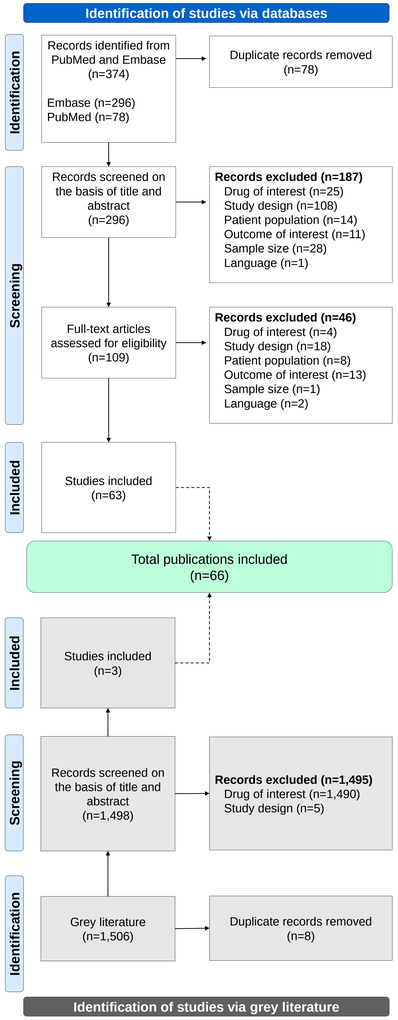
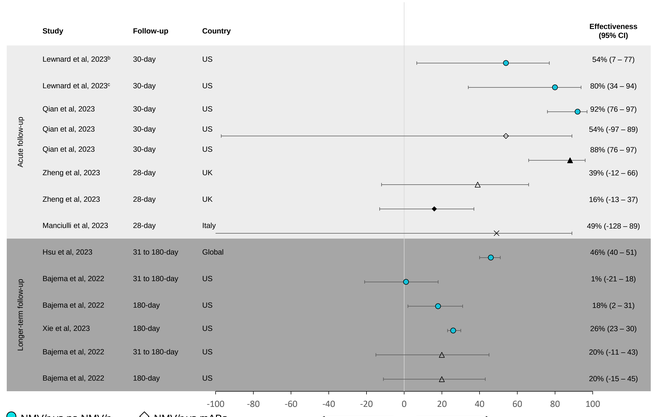


Table 1. Population-intervention-comparators-outcomes-study design criteria

Domain	Inclusion	Exclusion
Population	Adult and pediatric patients (12 years of age and older) diagnosed with mild-to-moderate COVID-19 (not on supplemental oxygen), who are at high or increased risk for progression to severe COVID-19, including hospitalization and death	Studies not reporting on any of the populations specified in the inclusion criteria
Interventions	Nirmatrelvir-ritonavir	Studies not reporting on any of the interventions specified in the inclusion criteria
Comparators	• No treatment • Best supportive care or standard of care • Active comparator, or any intervention recommended for the outpatient treatment of mild-to-moderate COVID-19	Studies not reporting on any of the comparators specified in the inclusion criteria
Outcomes	• Effectiveness against hospitalization • Effectiveness against mortality • Effectiveness against a composite endpoint of hospitalization and mortality	Studies not reporting on any of the outcomes specified in the inclusion criteria
Study Design	• Database analyses • Cohort studies • Retrospective and prospective observational studies, • Case series studies, • Registry analyses, • Descriptive studies, • Non-randomized or non-controlled studies, • Surveys	Network meta-analyses, systematic reviews, animal studies, pharmacokinetic or pharmacodynamic studies, commentary, editorials, errata, letters or notes, randomized controlled trials (RCTs), economic modeling, economic evaluations, guidelines
Publication Date	December 22, 2021 to March 31, 2023	Studies published prior to December 22, 2021 or after March 31, 2023

Figure 3. Effectiveness[a] Against All-cause Hospitalization or Mortality

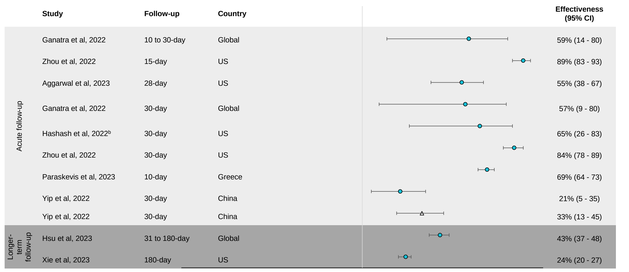


[a] Effectiveness is the percent reduction in odds/risk ratio and only studies that report an adjusted odd/risk are reported. Treatment effectiveness percentages were calculated by subtracting hazard ratios or odds ratios from 1 and multiplying by 100. Data in the figures are from each study, no statistical analysis was conducted across the studies. Only results that show NMV/r as a single intervention have been presented. [b] Population includes all patients, regardless of symptom onset. [c] Population includes patients who received NMV/r treatment within 5 days of symptom onset.

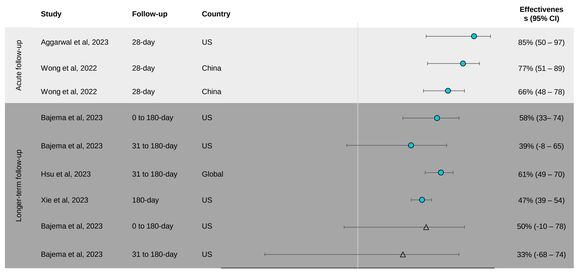
Note: The "no NMV/r" cohort varied in the studies. The following definitions were used for "no NMV/r": Qian et al. used "no NMV/r, molnupiravir, monoclonal antibodies, remdesivir, or combination"; Xie et al. used "did not receive other outpatient COVID-19 antiviral or antibody treatments within 30 days of the index date"; Bajema et al. used "did not receive NMV/r or molnupiravir"; Lewnard et al. and Hsu et al. stated "not receiving NMV/r."

Figure 2. Effectiveness[a] Against (A) All-cause Hospitalization and (B) All-cause Mortality

A) All-cause Hospitalization



B) All-cause Mortality



[a] Effectiveness is the percent reduction in odds/risk ratio and only studies that report an adjusted odd/risk are reported. Treatment effectiveness percentages were calculated by subtracting hazard ratios or odds ratios from 1 and multiplying by 100. Data in the figures are from each study, no statistical analysis was conducted across the studies. Only results that show NMV/r as a single intervention have been presented. [b] No NMV/r group is limited to patients with no inflammatory bowel disease

Note: The "no NMV/r" cohort varied in the studies. In **Figure 2A**., the following definitions were used for "no NMV/r": Yip et al., Hashash et al., and Zhou et al. used "not prescribed NMV/r or molnupiravir"; Ganatra et al. used "did not receive ritonavir, nirmatrelvir, tixagevimab-cilgavimab, bebtelovimab, bamlanivumab, molnupiravir, or convalescent plasma transfusion"; Xie et al. used "did not receive other outpatient COVID-19 antiviral or antibody treatments within 30 days of the index date"; Hsu et al., Paraskevis et al., and Aggarwal et al. stated "not receiving NMV/r." In **Figure 2B**., the following definitions were used for "no NMV/r": Xie et al. used "did not receive other outpatient COVID-19 antiviral or antibody treatments within 30 days of the index date"; Bajema et al. and Wong et al. used "did not receive NMV/r or molnupiravir"; Aggarwal et al. and Hsu et al. stated "not receiving NMV/r."

References

1. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane. Accessed July 12, 2023, https://training.cochrane.org/handbook/current
2. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. Mar 29 2021;372:n71. doi:10.1136/bmj.n71

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