EPH173

Untreated risk of hospitalization and death in high-risk subgroups of a nirmatrelvir/ritonavir treatment-eligible population with mild-to-moderate COVID-19 in the United States: a systematic literature review

Kristen Migliaccio-Walle,[1] Tendai Mugwagwa,[2] Ashley S. Cha-Silva,[3] Cynthia L. Gong,[1] David Campbell,[1] Romina Quercia,[2] Tobias Bergroth,[4] David L. Veenstra,[1] Mendwas Dzingina[2]

[1]Curta Inc., Seattle, WA, USA, [2]Pfizer Ltd., Tadworth, Surrey, UK, [3]Pfizer Inc., New York, NY, USA, [4]Pfizer AB, Stockholm, Sweden, [5]Pfizer Inc., Collegeville, PA, USA

INTRODUCTION

- Nirmatrelvir/ritonavir (NMV/r) was EMA approved in January 2022 and FDA-approved in May 2023 as the first oral antiviral for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe acute COVID-19, including hospitalization or death.[1,2]
- Interpretation of published real-world untreated risks of hospitalization or death is challenging due to:
  - Heterogeneity in study design, population, methods, and definition of "high-risk" populations
  - Lack of accounting for inherent differences in treated vs. untreated patient populations in observational studies
- To date, no study has systematically reviewed the published real-world untreated risks of hospitalization or death in key high-risk subgroup populations in the Omicron variant era.
- **Understanding the real-world untreated risk of hospitalization or death in high-risk patients is crucial for the development of patient treatment plans and value assessment of NMV/r and interventions.**

OBJECTIVE

- To systematically characterize the untreated risk of hospitalization and death in real-world US clinical practice among key subgroups of patients at high-risk for progression to severe COVID-19 during the Omicron era as reported in the literature.

METHODS

OVERVIEW

- A systematic literature review was conducted using PubMed, Embase, MedRxiv, SSRN, relevant conference abstracts and grey literature to identify real-world evidence studies.
- A multi-step screening and review process implemented key selection criteria in Table 1.

TABLE 1. KEY SELECTION CRITERIA

TOPIC	INCLUSION
Publication Date	• December 21, 2021 – January 30, 2024
Population	• US population at high-risk of COVID-19 progression as defined by the Centers for Disease Control and Prevention (CDC) as eligible for treatment.[3] ✓ Adult and pediatric outpatients (12 years of age and older) diagnosed with mild-to-moderate COVID-19 who are at high or increased risk for progression to severe acute COVID-19, including hospitalization and death. ✓ A positive PCR test was not required to be included. • **Subgroups of interest were age (<50, 50+ years, 65+ years), vaccination status (full, boosted, partial, none), and immunocompromised (IC) status (yes, no).** • Studies reporting exclusively on a special population (e.g., patients with IBD, cancer patients, pregnancy, etc.) were excluded
Intervention	Nirmatrelvir/ritonavir (NMV/r)
Comparison	• No treatment • Best supportive care or standard of care
Outcomes	Primary: • Incidence of short-term (28-30 days) hospitalization (COVID-19 specific and all cause) Secondary: • 28-30 day all-cause hospitalization or death • 28-30 day all-cause death
Time	Studies reporting data from the Omicron period or later
Study Type	• Case/clinical series reports (n per arm ≥30) • Cross-sectional studies • Database analyses • Observational studies (prospective and retrospective) • Registry analyses • Peer-reviewed publications (including Letters to Editor with outcome data) • Preprints posted within the prior 6 months (included descriptively) • Congress abstracts or posters • Randomized controlled trials were excluded.

METHODS (continued)

DATA EXTRACTION ELEMENTS

- Baseline patient population and study characteristics were extracted from each study, along with the following key elements:
  - **Study measures**: observed risk (adjusted and non-adjusted), relative risk, absolute risk, hazard ratio, or odds ratio
  - **Study arms**: treatment received, whether the arms were matched, and dosing of medication, if applicable.
  - **Subgroup status**: age, COVID-19 vaccination status, and immunocompromised status.

CALCULATIONS & ANALYSES

- Untreated risk of hospitalization, death, and hospitalization or death outcomes were estimated using 3 approaches: 1) observed risk, 2) within-study adjusted risk, and 3) adjusted and standardized estimate.
- **Observed risk**: observed untreated risk as reported.
- **Within-study adjusted risk**: calculated within each study using NMV/r as a reference.
- **Adjusted and standardized risk**: estimated using the relative risk reduction (RRR) of 0.796 for all-cause hospitalization or death reported in Lewnard 2023.[7]
  - The adjusted and standardized risk estimate was as:

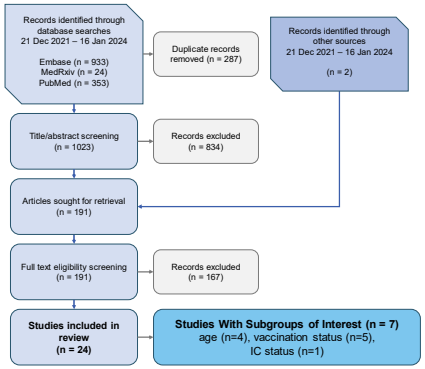
$$Control\ Event\ Rate = \frac{Experimental\ event\ rate}{1 - relative\ risk\ reduction} = \frac{0.70\%}{1 - 0.796} = 3.43\%$$

  - The Lewnard study followed the EPIC-HR trial design most closely, thus best approximating a high-risk target population in a real-world setting.
  - A relative risk reduction (RRR) of 0.796 for NMV/r versus untreated patients (hospitalization or death within 30 days of SARS-CoV-2 infection) was reported in this unselected population.
  - This RRR was applied across studies to calculate standardized estimates of untreated event risks for all-cause hospitalization and hospitalization or death.

RESULTS

- PRISMA diagram / study attrition is shown in Figure 1; studies were primarily retrospective using claims databases (e.g., TriNetX), or integrated health systems (e.g., Veterans Affairs)
- Most (n=22, 92%) were exclusively a US population; half explicitly reported on a predominantly Omicron period (n=12, 50%).
- Of the studies included, n=4 reported results by age; n=5 by vaccination status, and n=1 by immunocompromised status; these studies and characteristics are shown in Table 2.
- The adjusted and standardized risk for each outcome are shown in Table 3.

FIGURE 1. PRISMA DIAGRAM AND STUDY ATTRITION



RESULTS (continued)

TABLE 2. STUDY CHARACTERISTICS AND OUTCOMES INCLUDED

Author Year	Data Source	Study Type	Geography	Study Period	Subgroups	Outcomes
Shah 2023[4]	Cosmos	Single cohort	US	Apr 2022 - Aug 2022	Age <50 years Age 50+ years Vaccination – Full Vaccination – Partial Vaccination – None	Hospitalization
Xie 2023[5]	VA	Matched cohort	US	Jan 2022 - Nov 2022	Vaccination – Full Vaccination – Partial Vaccination – None	Hospitalization or Death
Dryden-Petersen 2023[6]	MGH Health	Unmatched cohort	US – Massachusetts / Southern NH	Jan 2022 - Jul 2022	Age 50+ years	Hospitalization or Death
Lewnard 2023[7]	Kaiser Permanente SoCal (KPSC)	Matched cohort	US - Southern California	Apr 2022 - Oct 2022	Vaccination – Full Vaccination – Partial	Hospitalization or Death
Butt 2024[8]	VA COVID-19 Shared Data - primary	Matched cohort	US	Jan 2022 - Feb 2023	Vaccination – Full Vaccination – Boosted Vaccination – Partial	Hospitalization or Death
Al-Obaidi 2023[9]	Banner Cerner-EHR	Matched cohort	US - Western US	Jun 2022 - Oct 2022	Vaccination – Full Vaccination – Partial	Hospitalization or Death
Lin 2023[10]	Cleveland Clinic	Matched cohort	US - Cleveland, OH	Apr 2022 - Feb 2023	Age 50+ years	Death

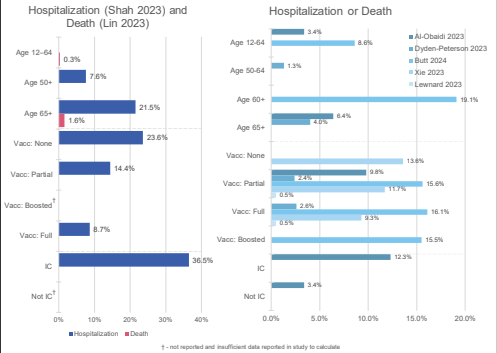
TABLE 3. RISK OF EACH OUTCOME AT 30 DAYS BY SUBGROUP

Subgroup	Stratification	Hospitalization		Death		Hospitalization or Death		
		Adj	A + S	Obs	A + S	Observed	Adjusted	Adj + Standardized
Age Group	Age 12–64	–	–	0.3%	0.3%	–	–	–
	Age <60	–	–	–	–	1.8%	2.0%, 2.5%	8.6%
	Age <65	–	–	–	–	0.7%	0.9%	3.4%
	Age 50–64	–	–	–	–	0.3%	–	1.3%
	Age 50+	3.9%	7.6%	–	–	1.3%, 3.9%	0.5%, 0.7%	–
	Age 65+	8.3%	21.5%	2.4%	1.6%	0.8%	1.5%	4.0%, 6.4%
	Age >60	–	–	–	–	3.9%	7.6%, 7.8%	19.1%
Vaccination Status	Vaccinated - None	9.6%	23.6%	–	–	2.8%	4.6%	13.6%
	Vaccinated - Partial	5.9%	14.4%	–	–	0.1%, 0.5%, 2.0%, 2.4%, 3.2%	1.0%, 2.5%, 3.7%, 5.8%, 6.2%	0.5%, 2.4%, 9.8%, 11.7%, 15.6%
	Vaccinated - Boosted	–	–	–	–	3.2%	5.8%, 5.9%	15.5%
	Vaccinated - Full	3.6%	8.7%	–	–	0.1%, 0.5%, 1.9%, 3.3%	0.8%, 3.0%, 5.1%, 5.8%	0.5%, 2.6%, 9.3%, 16.1%
IC Status	IC	–	36.5%	–	–	2.5%	1.2%	12.3%
	Not IC	–	–	–	–	0.7%	0.6%	3.4%

KEY: Adj – adjusted; A + S – adjusted and standardized; IC – immunocompromised; Obs – observed

- Hospitalization risk was highest among
  - Older patients (age ≥ 65: 21.5%) and immunocompromised patients (36.5%) regardless of vaccination status
  - Unvaccinated patients (23.6%)
- Risk of death (adjusted and standardized) was **5.3x higher** among older patients (age ≥ 65: 1.6%) than those aged 12-64 years (0.3%).

FIGURE 2. ADJUSTED AND STANDARDIZED RISK BY SUBGROUP



† - not reported and insufficient data reported in study to calculate

CONCLUSIONS

For untreated patients at high-risk for progression to severe acute COVID-19:

High-risk subgroups (older age, IC status, and unvaccinated) are more likely to experience either hospitalization or death.

The composite risk of hospitalization or death was highest among those aged >60 (19.1%) and IC (12.3%).

Understanding these risks among key untreated subgroups contextualizes the value of current antivirals and guides patient care planning.

LIMITATIONS

- This review was limited to studies that reported subgroups of interest as a component of a study in the overall high-risk COVID-19 population. This underrepresents the full subgroup literature and must be viewed as *hypothesis generating*.
- Studies were heterogeneous in design and population which could not be fully adjusted for given the small number of studies included, thus results are reported *descriptively* and must be interpreted with caution.
- Further evaluation of the broader literature of the untreated risk of hospitalization and death in high-risk sub-populations is therefore warranted.

REFERENCES

1. Kip KE et al. *Ann Intern Med*. 2023;176(4):496-504.
2. Zhou X et al. *bioRxiv*. Published online September 14, 2022. doi:10.1101/2022.09.13.22279908
3. Centers for Disease Control and Prevention. December 20, 2024. https://www.cdc.gov/covid/hcp/clinical-care/outpatient-treatment.html
4. Shah MM et al. *Am J Transplant*. 2023;23(1). doi:10.1016/j.ajt.2022.12.004
5. Xie Y et al. *BMJ*. 2023;381:e073312.
6. Dryden-Peterson S et al. *Ann Intern Med*. 2023;176(1). doi:10.7326/m22-2141
7. Lewnard JA et al. *Lancet Infect Dis*. 2023;23(7). doi:10.1016/s1473-3099(23)00118-4
8. Butt AA et al. *J Infect Dis*. 2024 Jan 12;229(1):147-154. PMID: 37711076; PMCID: PMC10786260.
9. Al-Obaidi et al. *Am J Med*. 2023;136(6). doi:10.1016/j.amjmed.2023.02.022
10. Lin DY et al. *JAMA Netw Open*. 2023;6(9). doi:10.1001/jamanetworkopen.2023.35077

DISCLOSURE

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Additional details and references available via QR code.

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