CO56

Baseline (Untreated) Risk of Hospitalization and Mortality in Patients with Specific Comorbid High-Risk Conditions who are Eligible for Nirmatrelvir/Ritonavir Treatment: A Systematic Literature Review Expansion Study

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INTRODUCTION

- A systematic literature review (SLR) was needed to understand the untreated risk of severe COVID-19 outcomes in adults with mild-to-moderate disease at high risk of progression (high-risk populations).
- Understanding baseline risk across key high-risk subgroups is critical to inform treatment decision-making. These insights support evaluation of the clinical value of nirmatrelvir/ritonavir (NMV/r) and access decisions of high-risk populations.

OBJECTIVE

This SLR aims to characterize the untreated risk of hospitalization and mortality among high-risk COVID-19 patients with specific pre-existing comorbidities during the Omicron era in real-world settings.

METHODS

- A global SLR of real-world studies (PubMed, Embase, and MedRxiv) was conducted to assess 28-30-day risks of all-cause hospitalization, mortality, and composite outcomes in NMV/r-eligible, high-risk COVID-19 patients (≥12 years & specific pre-existing comorbidities).
- To address potential confounding between groups and within-study heterogeneity, both observed (unadjusted) risks and calculated within-study adjusted risks (derived by applying the reported treatment effect to the NMV/r risk) were reported.

Table 1. Key Inclusion/Exclusion Criteria

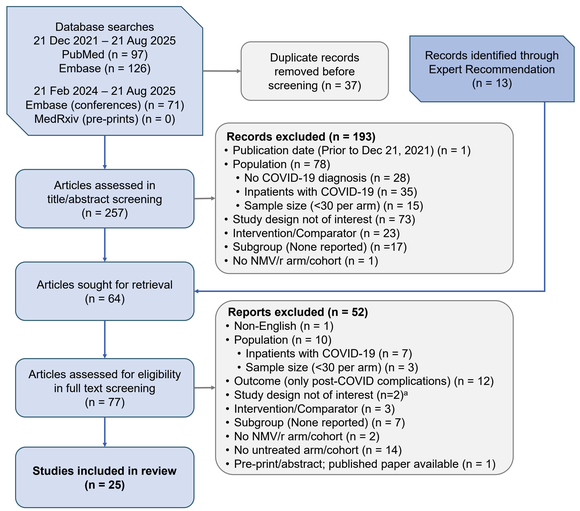
Category	Inclusion Criteria	Exclusion Criteria
Population	Adult and adolescent patients (≥12 years of age) with mild-to-moderate COVID-19, who are at high risk for progression to severe COVID-19, including hospitalization and death.	· Studies exclusively in patients <12 years of age · Inpatient population
Population Subgroups	Subgroups are based on the WHO 2023 definition of those at moderate- to high-risk for hospitalization from COVID-19. · Advanced age (>50 years; >65 years), cancer (current diagnosis), cardiovascular disease (CVD), chronic kidney disease (CKD) or chronic liver disease (CLD), chronic respiratory or cardiopulmonary disease (CPD), dementia (DEM), diabetes mellitus (DM), immunocompromised (IC) status, overweight / obesity (OB), smoking, medical technology dependence	Any study that is exclusively in a population not specified in the inclusion criteria
Intervention	NMV/r	Studies not reporting any information on NMV/r to ensure exclusion of patients not eligible or contraindicated to NMV/r
Comparators	· No treatment · Best supportive or standard of care	Studies not reporting on any of the comparators
Outcomes	Short-term (28-30-day): · Hospitalization (COVID-19 and all-cause) · All-cause hospitalization or death · All-cause death	· Outcomes not specific to COVID-19 infection · Outcomes not reported as: incidence or cumulative risk, relative risk (reduction), risk difference, odds ratio, risk ratio, rate ratio, hazard ratio
Study Designs	· Epidemiological, surveillance, retrospective database studies · Case-control and cross-sectional studies · RWE studies (prospective/retrospective observational studies)	· Non–RWE studies (RCT, case reports) · Editorials or opinion pieces · Implementation projects, protocols, or educational programs
Sample Size	≥30 patients per study arm	<30 patients per study arm
Geography	Global	None
Language	English language articles and abstracts	Articles in languages other than English
Dates of Publication	· Dec 21, 2021, to Aug 21, 2025 (articles) · Feb 21, 2024, to Aug 21, 2025 (abstracts) · Feb 21, 2025, to Aug 21, 2025 (pre-prints)	Studies conducted prior to December 21, 2021

RESULTS

Search Results

- A total of **25** studies met the inclusion criteria and were included in the review (**Figure 1**).
- Studies were excluded based on a predefined hierarchical set of exclusion criteria, as illustrated in the PRISMA flow diagram.

Figure 1. PRISMA Diagram and Study Attrition



Footnote
[a] Both records were SLRs/MAs and did not include any additional primary studies.

COVID-19-Related Hospitalization Risk

Observed COVID-19 related hospitalization risk was reported by 4 studies; within-study adjusted risk was calculated for 2 studies (**Table 2**).

Table 2. Untreated COVID-19-Related Hospitalization Risk

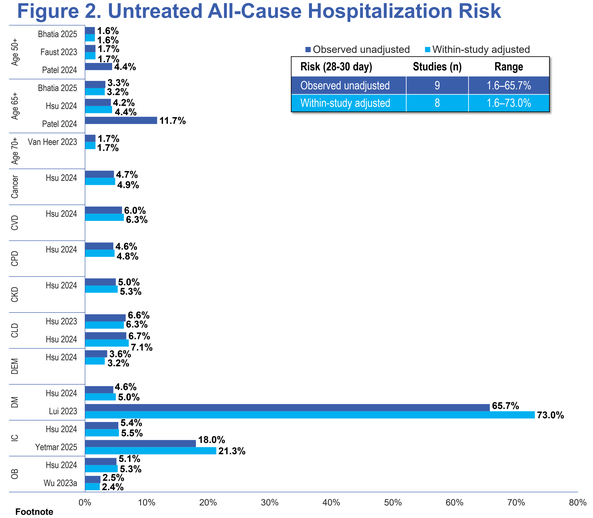
	Observed Unadjusted Risk		Within-study Adjusted Risk	
Groups	Studies (n)	Range	Studies (n)	Range
Overall	4	0.4–5.0%	2	0.6–1.9%
Age >50 years	2	0.4-2.1%	NR	NR
Age ≥60 years	1	0.8%	1	0.8%
Age ≥65 years	3	1.1-5.0%	1	1.5%
CVD	2*	1.6%	1	1.9%
CPD	2*	1.0%	NR	NR
Diabetes	2*	0.7%	1	0.6%

Footnote
Pinargote-Celorio 2024 reported a 90-day untreated COVID-19-related hospitalization risk of 21.5% in an immunocompromised population; however, this study was excluded from the primary analysis as the follow-up period fell outside the 28–30-day outcome of interest.

All-Cause Hospitalization Risk

Observed unadjusted all-cause hospitalization risk was reported by 9 studies and within-study adjusted risk was calculated for 8 studies (**Figure 2**).

Figure 2. Untreated All-Cause Hospitalization Risk



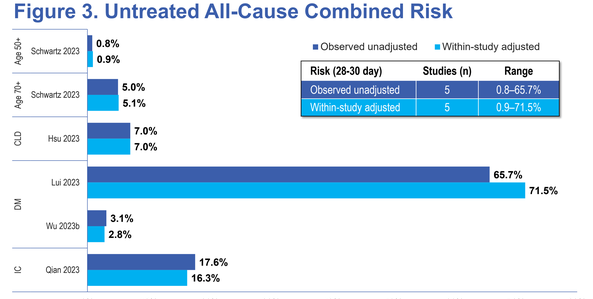
Risk (28-30 day)	Studies (n)	Range
Observed unadjusted	9	1.6–65.7%
Within-study adjusted	8	1.6–73.0%

Footnote
- The reported all-cause hospitalization risk estimates from one study were excluded from the primary analysis because they represented subcategories of predefined high-risk subgroups (e.g., compensated and decompensated liver cirrhosis; Hsu 2023).
- Van Heer 2023 study reported the observed untreated risk of all-cause hospitalization at 35 days and was included in the analysis.
- Pinargote-Celorio 2024 reported a 90-day untreated all-cause hospitalization risk of 30.2% in an immunocompromised population and was excluded from the primary analysis as the follow-up period fell outside the 28–30-day outcome of interest.

All-Cause Combined Hospitalization/Mortality Risk

Observed all-cause combined risk was reported by 5 studies and within-study adjusted risk was calculated for 5 studies (**Figure 3**).

Figure 3. Untreated All-Cause Combined Risk



Risk (28-30 day)	Studies (n)	Range
Observed unadjusted	5	0.8–65.7%
Within-study adjusted	5	0.9–71.5%

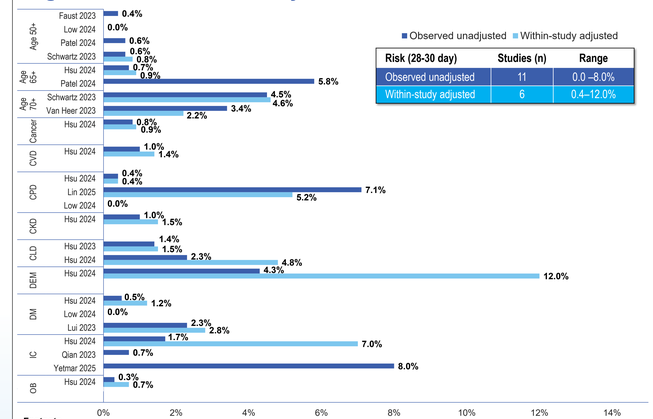
Footnote
- Two studies were excluded from the primary analysis as they reported the untreated risk of all-cause combined outcome of hospitalization or mortality for the subcategories of predefined high-risk subgroups (Hsu 2023: compensated and decompensated liver cirrhosis; Hsu 2023 and Chen 2024: CKD stage 3-5 and end stage CKD).
- Two additional studies reporting composite outcomes including emergency department (ED) visits were excluded, as ED events were outside the combined outcome of interest (Wu 2024 and Wu 2023a).

RESULTS (continued)

All-Cause Mortality Risk

Observed all-cause mortality unadjusted risk was reported by 11 studies and within-study adjusted risk was calculated for 6 studies (**Figure 4**).

Figure 4. All-Cause Mortality Risk



Risk (28-30 day)	Studies (n)	Range
Observed unadjusted	11	0.0 –8.0%
Within-study adjusted	6	0.4–12.0%

Footnote
- One study was excluded from the primary analysis as it reported the untreated risk of all-cause mortality for the subcategories of predefined high-risk groups (Hsu 2023: compensated and decompensated liver cirrhosis).
- Two studies reporting 90-day mortality risk were excluded from the primary analysis (Guermazi 2024, Pinargote-Celorio 2024).
- Van Heer 2023 reported the observed untreated risk of all-cause mortality at 35 days.

CONCLUSIONS

- **Across 25 studies conducted during the Omicron period, untreated COVID-19 patients within key high-risk subpopulations continue to face clinically meaningful risk of severe outcomes, including hospitalization and mortality.**
- **This data demonstrate that people with certain high-risk conditions remain at significant risk of hospitalization and death during the Omicron era, reinforcing the ongoing need for timely access to treatment.**

References (abbreviated):
Arbel. *N Engl J Med*. 2022; Bhatia. *PLoS Med*. 2025; Chen. *Expert Rev Anti Infect Ther*. 2024; Cheuk-Fung. *CID*. 2023; Dormuth. *JAMA Netw Open*. 2023; Faust. *Clin Infect Dis*. 2023; Guermazi. *Support Care Cancer*. 2024; Hsu. *Expert Rev Anti Infect Ther*. 2023; Hsu. *Expert Rev Anti Infect Ther*. 2024; Jorda. *Clin Microbiol Infect*. 2025; Lin. *Respir Res*. 2025; Low. *Int J Infect Dis*. 2023; Low. *Real World Outcomes*. 2024; Lui. *JAMA Netw Open*. 2023; Najjar-Debbiny. *Clin Infect Dis*. 2023; Patel. *Curr Med Res Opin*. 2024; Pinargote-Celorio. *J Antimicrob Chemother*. 2024; Qian. *Lancet Rheumat*. 2023; Schwartz. *CMAJ*. 2023; Van Heer. *Lancet Reg Health West Pac*. 2023; Wang. *J Infect Public Health*. 2025; Wei. *Emerg Microbes Infect*. 2025; Wu. *Int J Antimicrob Agents*. 2023a; Wu. *J Med Virol*. 2023b; Yetmar. *J Med Virol*. 2025.

Abbreviations:
CVD = cardiovascular disease; CPD = cardiopulmonary disease; CKD = chronic kidney disease; CLD = chronic liver disease; DEM = dementia; DM = diabetes mellitus; ED = emergency department; IC = immunocompromised; MA = meta-analysis; NMV/r = nirmatrelvir/ritonavir; NR = not reported; OB = obesity; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial; RWE = real-world evidence; SLR= systematic literature review; WHO = World Health Organization.

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Presented at ISPOR 2026; May 17–20, 2026; Philadelphia, PA, USA