

# Severity of COVID-19 Omicron Variants: A Global Systematic Review

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## INTRODUCTION

- As new SARS-CoV-2 variants continue to emerge, there is a persistent need for updated evidence on the clinical manifestations, severity, and overall burden of COVID-19.
- This evolving knowledge base is essential to guide prevention strategies, assess the impact on healthcare systems, and inform evidence-based treatment decisions.

## AIM

- To compare measures of disease severity such as hospitalization, intensive care unit (ICU) admission and mortality between SARS-CoV-2 variants of concern since Omicron's emergence.

## METHODS

- The SLR was registered a-priori with PROSPERO (ID: CRD42024619193), and the search conducted according to the Cochrane handbook for systematic reviews following the PRISMA guidelines.
- EMBASE® and MEDLINE® databases were searched for relevant publications on November 26, 2024, using the OVID platform.
- Supplemental grey literature searches encompassing ESCMID and IDWeek congresses from January 1, 2022, to December 31, 2024, were conducted on April 1, 2025.
- Two independent reviewers screened titles and abstracts, then full text publications of citations retrieved from the database searches against Population, Exposure, Comparisons, Outcomes (PECO) eligibility criteria.
- Inclusion criteria included adults infected with any of the following SARS-CoV-2 variants: BA.4, BA.5, BQ, BA.2.75, BA.2.86, XBB, EG.5, JN.1, KP.2, KP.3 and XEC. Comparisons of interest were between variants of concern; and outcomes included hospitalization, ICU admission, mortality, organ support, or composite measures of disease severity, including adjusted data metrics.

## RESULTS

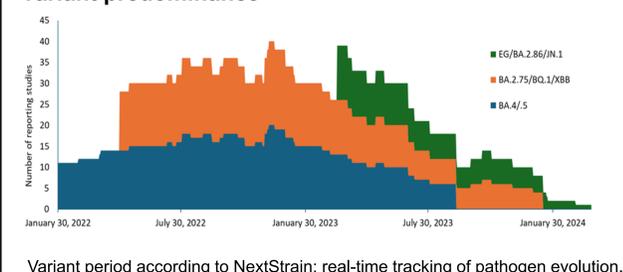
- A total of 1,988 records were identified with 32 unique records included (Table 1; Figure 1).

Table 1. Overview of study characteristics (N=33)

Characteristic	Pubs, N (%)
<b>Study design</b>	
Cross-sectional	2 (6)
Prospective cohort	7 (21)
Retrospective cohort	21 (64)
Case-control	2 (6)
<b>WHO region</b>	
Americas	13 (39)
Eastern Mediterranean	1 (3)
European	9 (27)
South-East Asia	4 (12)
Western Pacific	6 (18)
<b>SARS-CoV-2 variant</b>	
BA.4	11 (33)
BA.5	23 (70)
BA.2.75	4 (12)
BN.1	1 (3)
BQ	10 (30)
XBB	24 (73)
EG.5	4 (12)
BA.2.86	5 (15)
JN.1	1 (3)
KP onwards	0 (0)
<b>SARS-CoV-2 variant measurement method</b>	
Defined by study	12 (36)
author/external source	21 (64)
Variant sequenced	21 (64)
<b>Outcomes reported*</b>	
Composite disease severity†	13 (39)
Hospitalization	16 (48)
ICU	12 (36)
Mortality	17 (51)
Organ support‡	10 (30)

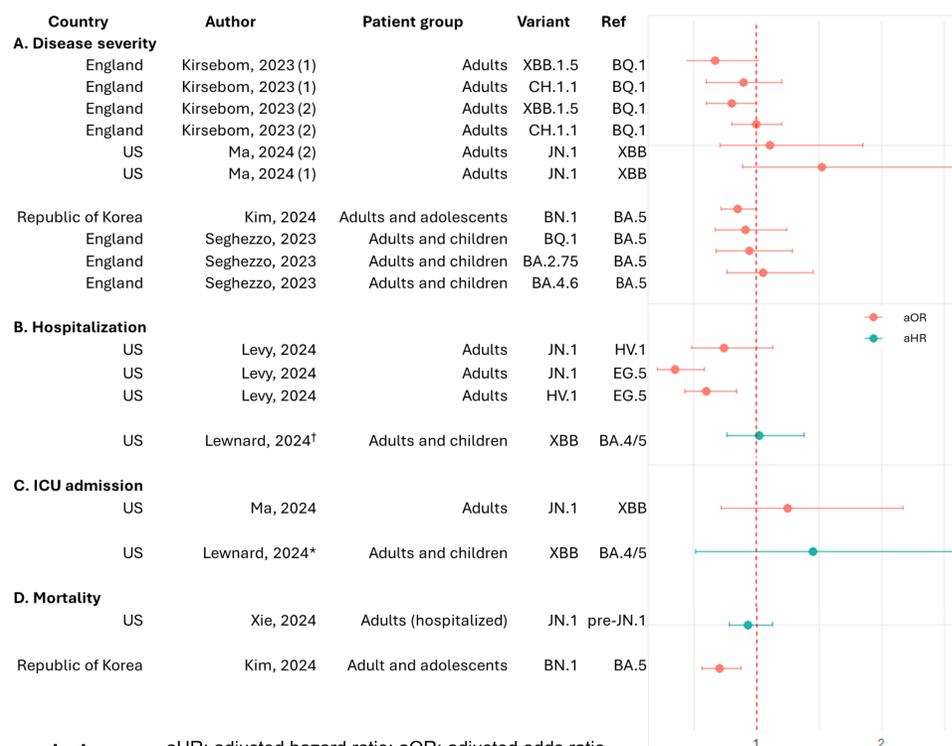
ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization. Variants listed in chronological order of emergence. \*Included studies may have reported multiple variants/outcomes, therefore total and proportion exceeds total number of studies/100%.

Figure 1. Number of studies reporting during periods of BA.4/5, BA.2.75/BQ.1/XBB, and EG.5/BA.2.86/JN.1 variant predominance



- Adjusted results were reported regarding the impact of BA.2, BA.4, BA.5, BN.1, BQ.1, CH.1.1, JN.1, HV.1 and XBB subvariants on disease severity/composite outcomes (n=6), hospitalization (n=6), mortality (n=6), ICU admission (n=2), and oxygen therapy (n=1).
- According to odds ratios (OR), risk of hospitalization, ICU admission, mortality, and disease severity were comparable across recent Omicron variants, compared to their respective comparators of earlier variants (Figure 2).

Figure 2. Direct Comparison by Variant Period of Hospitalization based on Outcomes (A), Composite measures of disease severity, 1-4 (B), Hospitalization, 5,6 (C), ICU admission, 4,5 and (D), Mortality 2,7



aHR: adjusted hazard ratio; aOR: adjusted odds ratio.

\*Composite outcomes were: *Kirsebom* (2023) – Risk of ICU admission or death; *Ma* (2024) Invasive mechanical ventilation or death, Advanced respiratory support - new receipt of high-flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation; *Kim* (2024) – Receiving care in a medical facility and was considered at risk of mortality (patients required therapeutic interventions such as non-invasive or invasive ventilation, high-flow oxygen therapy, extracorporeal membrane oxygen, or continuous renal replacement); *Seghezzo* (2023) – hospital admission or death; †*Lewnard* (2024) upper confidence limit is equal to 4.13 (beyond axis bounds).

- Five studies stratified outcomes by extent of comorbidity (e.g., number, specific conditions, Charlson Comorbidity Index score). Across all assessed periods, comorbidities were statistically significant predictors of worse outcomes among patients with COVID-19.

## CONCLUSIONS

- Overall, COVID-19 disease severity was comparable among Omicron subvariants.
- Further research is warranted to expand the available evidence base, particularly for later Omicron subvariants such as KP.2, LP.8.1, NB.1.8.1, and XFG, as no relevant publications were identified in this systematic review.
- A meta-analysis to generate pooled estimates of variant effect was considered. However, the heterogenous study populations, exposures and outcome definitions led to too few comparable studies to support a robust synthesis.
- The continued evolution of SARS-CoV-2 variants highlights the importance of continued vaccination campaigns with updated COVID-19 vaccines to better match circulating strains, and prompt use of antiviral treatment for eligible patients.

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## Disclosures

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