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RAPID REVIEW SYNTHESIS:

COVID-19: Omicron variant and risk factors for severe disease

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Key Messages

The purpose of this rapid synthesis was to identify research that examines which individual risk factors may predict hospitalization, serious illness, and death after infection with the Omicron variant of SARS-CoV-2. The rapid synthesis is based on a literature search in Medline, Embase and Cochrane's COVID-19 register. Two researchers independently reviewed the search results and selected studies for inclusion.

The literature search resulted in 392 unique records, but only one study met the inclusion criteria. The included study used data from a Swedish registry-and compared confirmed cases of COVID-19 from different phases of the pandemic. The study showed that after infection with the Omicron variant:

- Unvaccinated individuals who have not previously been infected with SARS-CoV-2 have a higher risk of serious illness than vaccinated people. Gender, age and number of comorbidities may increase the risk of serious illness. The risk of serious illness in unvaccinated in men aged 40-64 years with two or more comorbidities is 12 percent.
- The risk of severe COVID-19 among vaccinated people younger than 65 years is low for men and women, even for people with comorbidities.
- The risk of severe COVID-19 may be increased among vaccinated people above 65 years, but this only applies to people who also have one or more comorbidities.

Only one study met inclusion criteria; there is a lack of data assessing which individual risk factors and comorbidities have the greatest impact on the risk of serious illness after infection with the omicron variant of SARS-CoV-2.

Title:
COVID-19: Omicron variant and risk factors for severe disease – a rapid evidence synthesis

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Publisher:
Division for Health Services at the Norwegian Institute of Public Health has conducted the review based on an internal commission from Division for Infection Control

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Updated:
Last search for studies: March 2022

Peer review:
Kristian Rødland, Senior medical officer, NIPH

Hovedbudskap

Hensikten med denne hurtigoversikten har vært å identifisere forskning som undersøker hvilke individuelle risikofaktorer som kan predikere sykehusinnleggelser, alvorlig sykdom og død etter smitte med Omikron-varianten av SARS-CoV-2. Hurtigoversikten er basert på litteratursøk i Medline, Embase og Cochranes covid-19 register. To forskere gikk gjennom søkeresultatene og valgte ut studier for inklusjon.

Litteratursøket resulterte i 392 unike treff, men bare én studie tilfredsstilte inklusjonskriteriene. Den inkluderte studien var en svensk registerbasert studie som sammenliknet bekreftede tilfeller av covid-19 fra ulike faser av pandemien. Studien viste:

- Etter omikron-smitte har uvaksinerte førstegangssmittede høyere risiko for alvorlig sykdom enn vaksinerte. Risiko for alvorlig sykdom ser ut til å avhenge av kjønn, alder og antall tilleggssykdommer (komorbiditet). Uvaksinerte menn i aldersgruppen 40-64 år med to eller flere tilleggssykdommer har ca. 12 prosent risiko for alvorlig sykdom.
- Etter omikron-smitte er risiko for alvorlig covid-19 blant vaksinerte som er yngre enn 65 år lav for begge kjønn, selv for personer med tilleggssykdommer.
- Etter omikron-smitte er risiko for alvorlig covid-19 forhøyet blant vaksinerte som er 65 år og eldre som også har èn eller flere tilleggssykdommer.

Vi har ikke identifisert studier eller data som gjør det mulig å vurdere hvilke individuelle risikofaktorer og tilleggs-sykdommer som har størst innvirkning på risiko for alvorlig sykdom etter smitte med omikron-varianten av SARS-CoV-2.

Tittel:
Covid-19: Omikron-variant og risikofaktorer for alvorlig sykdom – hurtigoversikt

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Hvem står bak denne publikasjonen?
Område for helsetjenester i Folkehelseinstituttet på oppdrag fra Område for smittevern

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Når ble litteratursøket avsluttet?
Mars 2022

Fagfellevurdering:
Kristian Rødland, overlege, FHI

Preface

This rapid synthesis is a follow-up to a previous rapid review "COVID-19 and risk factors for hospitalization, serious illness and death" published on 19th May 2021. In this follow-up, we focus exclusively on studies examining and reporting which individual risk factors can predict hospitalization, serious illness, and death after infection with the Omicron variant.

Kristian Rødland (senior medical officer, Norwegian Institute of Public Health) critically reviewed the protocol and the final report prior to publication. We thank our colleagues for important comments and feedback.

Background

By the time this report is written the World Health Organization (WHO) reports that "globally, there have been 492,189,432 confirmed cases of SARS-CoV-2, including 6,159,474 confirmed deaths, and a total of 11,250,782,214 vaccine doses administered" (1). The WHO European region reports that Norway has had 1,410,047 confirmed SARS-CoV-2 cases with 2,518 deaths from January 3, 2020 to April 5 2022 (1).

On November 26, 2021, the WHO declared a new variant called Omicron (B1.1.529) as a variant of concern (2). This variant is also known as the South African variant marking the place that first reported the rise in cases (i.e., outbreak in younger adults <30 years at Gauteng). This variant presents with several mutations in the spike protein, many of which are located within the receptor binding domain (3). Mutations may have an impact on how the virus behaves including spread and severity of illness. This means, for example, that the neutralizing potency of all COVID 19 vaccines might be reduced against this variant.

Initial evidence suggested that, as compared with previous variants of concern (Alpha, Delta, etc.), Omicron had increased transmissibility and increased resistance to vaccine induced immunity (4). Excluding some differences in the involvement of lower respiratory track (5), symptoms are similar to previous variants. The presence or absence of symptoms can be affected by vaccination status, age or other health conditions. The most common symptoms shown by Omicron-affected patients were fever or chills, severe fatigue, a scratchy throat, wet cough, runny nose, diarrhoea, headache, and other body aches, shortness of breath or difficulty breathing. SARS-CoV-2 real-time reverse-transcription polymerase chain reaction (RT-PCR) continue to detect the variant, however one of the three target genes called S gene is not detected (6).

Omicron infection generally caused less severe disease than infection with prior variants. One of the first reports came from a hospital in Tshwane, the centre of the Omicron outbreak in South Africa. The report showed that out of 42 patients in the ward on December 2, 2021, 29 (70%) were not on oxygen therapy, whereas 13 patients were dependent on supplemental oxygen and 9 had a diagnosis of COVID-19 pneumonia based on a combination of symptoms, clinical signs, chest X-ray, and inflammatory markers. The remaining four patients were on oxygen for other medical reasons (two previously on home oxygen, one for heart failure, and one with a confirmed diagnosis of pneumocystis pneumonia). There were only four patients in high care and one in the intensive care unit (ICU). The number of patients in high care on double oxygen, high-flow nasal oxygen, or on non-invasive ventilation was noticeably less in the Omicron wave (7).

It is unknown, however, whether the risk factors leading to hospitalizations, serious disease, or death, following infection with the Omicron variant, are the same as for previous variants.

Objectives

The overall objective of this rapid review was to examine the risk factors for disease severity for those infected with the Omicron variant. The research questions were:

1. What are the risk factors (clinical characteristics and predictors) for hospitalization, serious/critical COVID-19, or death following infection with the Omicron variant?
2. Are risk factors different between vaccinated and unvaccinated individuals*

*Fully vaccinated can be defined as two doses of any two-dose vaccine or one-dose of a single dose vaccine, and partially vaccinated is defined as a single dose of a two-dose vaccine. Where the vaccine brand (e.g., Moderna, AstraZeneca) is available, we will report it.

Methods

The conduct of this rapid review was guided by and reported according to the standards of the PRISMA Checklist (8). A protocol for this rapid review synthesis was developed and shared internally and with stakeholders who commissioned this work prior to the start of data abstraction and presented at the end of this document in Appendix 1. Stakeholders provided feedback prior to the initiation of the review.

Literature search

An experienced information specialist (supported by a peer reviewer) developed and conducted a comprehensive literature search. The information specialist (IH) conducted a systematic search in the Ovid MEDLINE, Embase (Ovid), and Cochrane COVID-19 register for articles, published protocols and trial registry records between November 2021 until March 16, 2022. The search was done using Medical Subject Headings (MeSH, in MEDLINE) and corresponding Emtree terms (in Embase) and the generic free-text search terms related to "omicron or omikron or B.1.1.529 or BA.1or BA.1.1 or BA.2 or BA.3 In Medline and Embase, we added Mesh and free-text terms corresponding to the outcome i.e. hospitalization, death, mortality, intensive or critical care or critical illness.-The search strategy is provided in Appendix 1.

The search terms were flexible and tailored to the electronic databases above. All studies published or registered from November 2021 until present were retrieved to assess their eligibility for inclusion in this study. The search was not restricted by languages. To find additional potentially eligible studies, reference lists of included citations were cross-checked.

If a trial registry record was available for a published study, we planned to associate the trial registry record to the published study, present it as one, and use it in the assessment of outcome reporting bias. Other type of trial registry records (completed and not yet published, ongoing, withdrawn), were thought to aid informing this rapid review, and the nature of upcoming studies.

Inclusion criteria

The inclusion criteria established for this review used a PECOS framework as Table 1 presents.

Table 1. PECOS framework

Population	Worldwide population. Individuals with a COVID-19 Omicron (B.1.1.529 or BA.2 lineage) diagnosis. COVID-19 cases should be defined by PCR/ antigen testing*
Exposure/risk factor	Omicron (B.1.1.529 or BA.2 lineage) and risk factors (for example age, sex, ethnicity, deprivation, body mass index, medical conditions, underlying comorbidities, as well as substance use).
Comparator	People without the investigated risk factors
Outcome(s)	Clinical severity of individuals with Omicron (B.1.1.529 or BA.2 lineage) variant. Hospital admission, ICU admission, ICU with ventilation, severe disease, death
Study design	Registry studies using data from databases or hospital which analyses the data according to a cohort or case control design. Use of a multivariate statistical model is desired.

ICU: intensive care unit

*PCR polymerase chain reaction (detection of viral material) or antigen test (detection of viral proteins) test performed on oro- and nasopharyngeal swabs and/or on respiratory-tract secretions and aspirates.

No other limitations were imposed on the search or study selection process. Both peer-reviewed and preprint papers were eligible for inclusion, as were papers written in Scandinavian, English or Spanish languages. We included trial registry records of any status (completed and published, ongoing, completed but unpublished, withdrawn), abstracts, and conference proceedings. Abstracts and conference proceedings were considered if they met PECO; we planned to place them under awaiting classification category.

Exclusion criteria

We excluded:

- Other diseases; SARS-CoV-2 infection variants (e.g., Alpha, Delta) as the main population group
- Laboratory (including genetic testing) and radiological findings used in clinical decision rules
- Podcasts, editorials, commentary, qualitative designed studies

Data extraction (selection and coding)

Study selection was done in duplicate (JB, AVF). All citations included by the title/abstract screening process were passed on to full text review. One researcher (JB) reviewed and summarized the studies selected in full text.

Risk of bias assessments

We planned to critically appraise the studies if they were case control or cohort designs with the Newcastle Ottawa Scale.

Synthesis

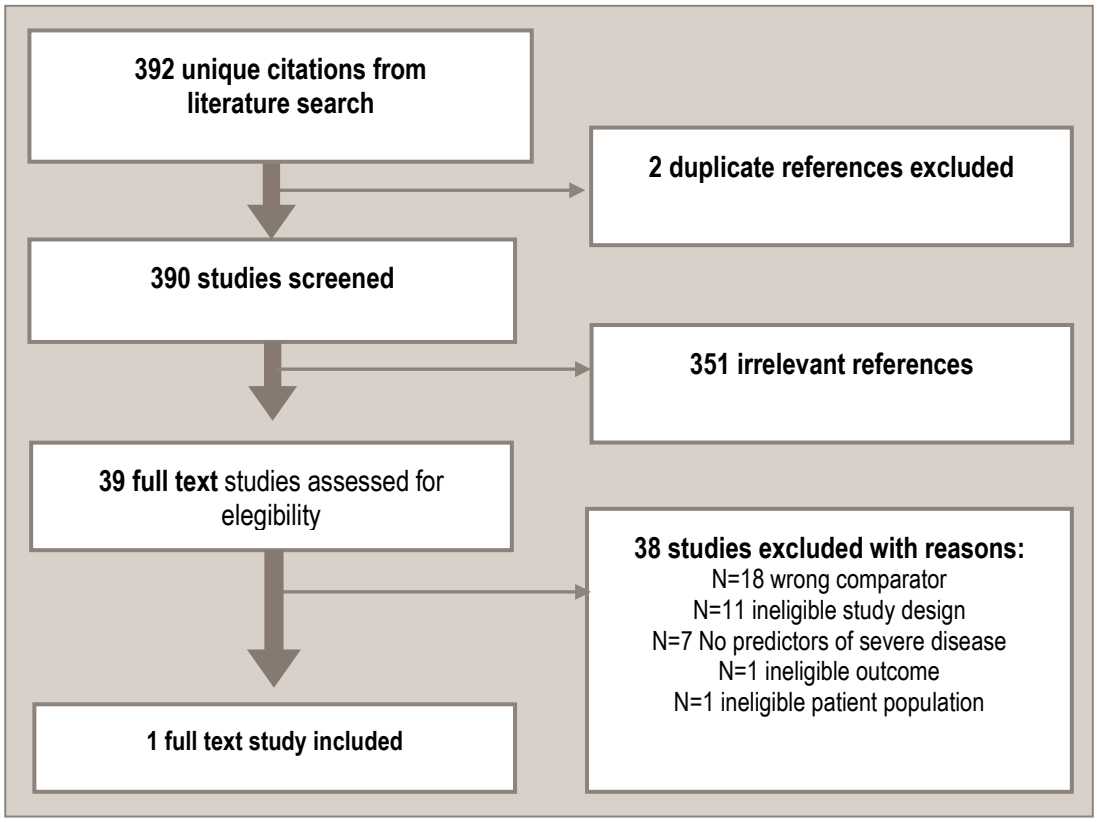
As this rapid review synthesis was conducted over a very short timeline and incorporated diverse evidence sources, no formal statistical or qualitative analysis was planned. Data from the included study are summarized narratively and in summary table and detailed table of results.

Results

Literature search

The searches returned a combine total of 392 titles and abstracts for further evaluation. A total of 351studies and trial registry records assessed at title and abstract citations were excluded, and 39 articles were passed to full-text screening. A further 38 articles were excluded during full-text screening (see Appendix 2) leaving 1 included (9), as illustrated in Figure 1. Although we only included one study, we have selected seven studies (10-16) containing some information of interest. Information on these seven studies is summarized in Appendix 3.

Figure 1. PRISMA study flow chart



Included study

This study was published in 2022, was written in English, and conducted in Sweden. We have summarized the characteristic of the included study, and inclusion and exclusion criteria in Tables 2 and 3. Kahn used the following definitions:

- *A case* was in all analyses defined as a person with a first-time positive test or any positive test for COVID-19 at least 90 days after a prior positive test.
- *Severe COVID-19* was defined as at least 24 h hospitalisation 5 days before until 14 days after a positive test and with a need of oxygen supply ≥5 L/min or admittance to an intensive care unit (ICU).
- Persons who had received at least two COVID-19 vaccine doses, irrespective of vaccine type, more than 7 days before the case date were classified as *vaccinated*, whereas persons with one or no doses were classified as *unvaccinated*.
- Low risk of severe COVID-19 was defined as <1.0%, high risk was defined as ≥5%.
- Comorbidities were defined as diagnoses in inpatient or specialized care during five years before baseline in the following disease groups: cardiovascular diseases, diabetes or obesity, kidney or liver diseases, respiratory diseases, neurological diseases, cancer or immunosuppressed states, and other conditions or diseases (Downs syndrome, HIV, sickle cell anemia, drug addiction, thalassaemia or mental health disorder).

Table 2. Characteristic of included study

Author year Design	Country Pub type Language	Population	Comparator/exposure	Outcome	Objective
Kahn 2022 (17) Cohort	Sweden Full text English	Individuals with SARS-CoV-19 residing in Scania, Sweden from 27 Dec 2020 until 25 Jan 2022	1) Delta period 2021 week 27–47. 2) Transition period 2021 week 48-51; 2021 week 48-51 when Omicron was first observed 3) Omicron as the dominating variant 2021 week 52 and week 1 2022	Hospitalization and disease severity among adults (vaccinated unvaccinated)	To monitor Omicron risks in risk groups defined by sex, age, and comorbidities in addition to vaccination status.

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• All persons residing in Scania (Skåne), southern Sweden (Swedish residents). • Analyses restricted to infections that occurred until Jan 9, 2022.	• Individuals who died or moved away from the region were censored on the date of death or relocation.

This study identified 55,269 coronavirus disease cases during the three periods investigated, of whom 437 (0.78%) were classified as severe. Unvaccinated cases were similar with respect to age, sex and comorbidities during the Delta and Omicron periods. Vaccinated cases during the Omicron period were younger and had fewer comorbidities than during the Delta period.

Authors used logistic regression adjusted for sex, age, comorbidities, and prior infection, and additionally for booster dose and time since last dose among the vaccinated.

- The estimated odds of severe COVID-19 were 40% lower (95% confidence interval (CI): 18–56% lower) among unvaccinated and 71% lower (95% CI: 54–82% lower) among vaccinated cases during the Omicron period than during the Delta period.
- The risk for severe COVID-19 remained high among unvaccinated, first-time infected cases of both sexes during the Omicron period in the age group 65 years and older (8.1% to 14.9% in women and 6.6% to 36.9% in men depending on number of comorbidities), and also among men in the age group 40–64 years with two or more comorbidities (11.9%).
- The risk of severe COVID-19 among vaccinated cases younger than 65 years was low for both sexes during Omicron, even in the presence of comorbidities.
- The risk of severe COVID-19 remained elevated among vaccinated cases 65 years and older during Omicron only in the presence of at least one (men) or at least two comorbidities (women).

Research in Progress.

No additional studies still in progress were identified. The trial registries search yield 126 records. We did not include any trial registry records.

Discussion

This rapid review aimed to address the question of the risk factors for disease severity for those infected with the Omicron variant (B.1.1.529). It is especially relevant given the current COVID-19 outbreaks globally including Norway.

We present findings from Khan (17) who showed lower risk of severe disease among the vaccinated. Vaccine effectiveness was seen by authors as changed from protection against both infection and severe disease from Delta to protection only against severe disease from Omicron. The risk of severe disease was also generally lower for unvaccinated cases during the Omicron period but remained high among older people and middle-aged men with comorbidities. Similarly, Public Health Ontario (18) reported Omicron infections could be considered severe, particularly in older age groups, individuals with comorbidities, and unvaccinated individuals.

Low risk according to vaccination status has been reported in other studies. The Los Angeles County Department of Public Health using COVID-19 surveillance and immunization registry data, explored COVID-19 hospitalization rates by COVID-19 vaccination status and variant predominance (19). They found during the Omicron period, unvaccinated persons had a hospitalization rate 23.0 times that of fully vaccinated persons with a booster and 5.3 times that of fully vaccinated persons without a booster. A retrospective cohort study from France investigated 149,064 COVID-19 cases, of which 497 had a serious hospital event (447 Delta, 50 Omicron), defined as admission to the ICU or admission to a critical care unit or death (20). Of the 826 Omicron cases with known vaccination status, 46.4% were vaccinated (7.8% having one dose, 67.1% two doses, 24.8% three doses, and 0.3% four doses). The UKHSA report that the risk of hospitalization is lower for Omicron cases after two and three doses of vaccine, with an 81% (77 to 85%) reduction in the risk of hospitalization after three doses as compared to unvaccinated Omicron cases (21).

The Norwegian Preparedness Registry individual data was used to estimate the risk of hospitalization for Omicron cases (39,524) compared with Delta cases (51,481), as well as the length of stay, risk of admission to an ICU and deaths (22). The reduced risk of hospitalization for Omicron as compared to Delta was smaller among cases who completed a primary vaccination schedule 7–179 days before their positive test, as compared with unvaccinated cases (66% for Omicron vs 93% for Delta with confidence interval that did not overlap). Having a third vaccine dose yielded a similar reduction in hospitalization risk for Omicron and Delta cases, compared to unvaccinated cases (86% and 88% respectively with overlapping confidence intervals). Of note, Omicron cases who had partially completed a primary vaccination series or who had completed primary vaccination with maximum two doses ≥ 180 days before positive test had no significant decrease in risk compared with unvaccinated.

Khan suggested that while the SARS-CoV-2 Omicron variant rarely leads to severe disease in vaccinated persons, first-time infection can still cause severe disease in unvaccinated persons with advanced age or underlying illnesses. Contrary to Khan's findings, a retrospective study by Wang (23) reported first time SARS-CoV-2 infections that occurred during the Omicron period were associated with significantly less severe outcomes than first-time infections during the Delta period. In addition, Butt et al (24) reports Omicron variant infection in children and adolescents to be associated with less severe disease than Delta variant infection as measured by hospitalization rates and need for ICU care or mechanical ventilation. A retrospective cohort study suggested among the children under 5 years old (unvaccinated) the overall risk of emergency department visits and hospitalization in the Omicron cohort were 3.89% and 0.96% respectively. Similar trends were observed for other paediatric age groups, adults (18 to 64) and older adults (23). However, although children comprised a larger proportion of Omicron cases (compared to other variants) does not necessarily mean that Omicron causes more severe disease in children (25).

The measurement of disease severity is not simple, and results must be interpreted with caution, as it may hinder our understanding of Omicron outcomes. The high transmissibility of Omicron resulted in record case numbers, which raised Omicron severity indicators such as emergency department visits, hospitalization, length of stay in a hospital, intensive care unit admission, and death (all proxies for disease severity), but have several limitations (18). Disease severity measured by hospital admission is not very specific as it does not indicate cause, and there can be a wide range of severity (26). Data from hospital admissions does frequently not differentiate between people admitted *because* of COVID-19 and those *who test positive on* wards during routine checks.

Some researchers have argued that intensive care unit bed occupancy is a better measure for disease severity arguing that bed occupancy with COVID is likely because of COVID rather than just with it. In this regard, research showed that compare to Delta variant, the Omicron variant is less likely to result in ICU admissions and pneumonia (27). When it does results in admissions Also inferring disease severity from daily or cumulative measure may be misleading because a higher number of deaths, hospital admissions or other metrics may result from an increase in infections, and not increased severity. A clear example is seen in children, were the metric of hospital admissions as a fraction of cases may not be a good measure, as it does not fully reflect more severe disease.

In addition, the early Omicron severity data is of limited validity due to patients with mild presentations possibly being more likely to be admitted in a hospital as a precaution, insufficient follow-up time for severe outcomes to accumulate, and not enough cases to properly represent entire populations (18).

Research Limitations

The study included in this review compared people with COVID 19 in different periods, and reflects people infected with different variants of the SARS-CoV-2 virus. The selection of participants may have affected the results as it is limited to a particular area of Sweden. The studies of interest included in Appendix 3 and the discussion used different methods to identify

Omicron cases including genome sequencing, local estimates of variants of interest epidemiology which cast doubts on the classification of cases as Omicron. The definitions of emergency visits or hospitalizations varied among the studies and thus the true burden and risk for some age groups described above may be misrepresented.

Review Limitations

There are limitations to the review methods employed here, however these methods were selected to tailor our approach to our knowledge user needs and satisfy the urgent need to provide timely results. There is also a chance that our literature search missed documents that could answer our question. However, we were unable to perform an exhaustive literature search due to the timelines imposed on this review.

Conclusion

The current evidence derived from one included study and few references of interest is not enough to conclude what are the risks factors (clinical characteristics and predictors) for disease severity associated with the Omicron variant infection. There are significant gaps in the literature, especially related to our outcomes of interests. However, the evidence supports efforts to increase vaccination uptake should thus remain a public health priority. The risk of severe outcomes seems to lessen with vaccination and booster doses. When time passes, a more complete picture of Omicron risks for disease severity will emerge.

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Appendix

Appendix 1. Project protocol

Title: Omicron variant and disease severity: a protocol for a rapid evidence synthesis

Review Question
The review question is two sided:

1. What are the risk factors (clinical characteristics and predictors) for hospitalization, serious/critical COVID-19, or death following infection with the omicron variant.
2. Are risk factor different between vaccinated and unvaccinated individuals.*

*Fully vaccinated can be defined as 2 doses of any 2-dose vaccine or 1 dose of a single dose vaccine, and partially vaccinated is defined as a single dose of a 2 dose vaccine. Were the vaccine brand (e.g. Moderna, AstraZeneca) is available we will report it; ICU: intensive care unit;

Searches
A systematic search will be performed in the Ovid MEDLINE and WHO COVID-19 Global literature on coronavirus disease database for articles between 15. Nov 2021 until present. The search will be done using Medical Subject Headings (MeSH, in MEDLINE) and the generic free-text search terms related to "COVID-19" AND "variant" AND "Omicron".
Text search terms related to "COVID-19" AND "variant" AND "Omicron" will be used.
The search terms will be flexible and tailored to the electronic databases above. All search hits will be retrieved to assess their eligibility for inclusion in this study. The search will not be restricted by languages. To find additional potentially eligible studies, reference lists of included citations will be cross-checked.
Other sources that will be searched: ClinicalTrials.gov and ICTRP (WHO). If available, associated trial registry records to a published study will be used to assess outcome reporting bias. Other type of trial registry records (completed and not published, ongoing, withdrawn) will aid informing the update of this rapid review, and the nature of upcoming studies.
The search strategy is included at the end of this document.

Condition or domain being studied
The fifth SARS-CoV-2 variant of concern, Omicron (B.1.1.529 or BA.2 lineage) and its consequences/severity.

Summary of Inclusion and exclusion criteria

	Included	**Excluded**
Population	All populations. Individuals with a COVID 19 Omicron (B.1.1.529 or BA.2 lineage) diagnosis.	Other diseases SARS-CoV-2 infections Delta, Delta-2 cohort, South Africa

	COVID-19 cases should be defined by PCR/ antigen testing*	
Setting(s)	Healthcare and non-healthcare settings	
Context	COVID-19 pandemic	Other diseases SARS-CoV-2 infections Delta, Delta-2 cohort, South Africa
Exposure	Omicron (B.1.1.529 or BA.2 lineage) risk factors (age, sex, ethnicity, deprivation, body mass index (i.e., BMI), medical conditions, underlying comorbidities, as well as substance us).	Clinical symptoms and laboratory-based risk factors were not included in this report.
Comparator	People without the investigated risk factors. Only studies where the relative importance of various risk factors were assessed using multivariate statistical models will be included	
Outcomes	Clinical severity of individuals with Omicron (B.1.1.529 or BA.2 lineage) variant. Hospital admission, ICU admission, ICU with ventilation, severe disease, death.	
Language	Scandinavian, English, Spanish	Any other languages
Publication Status	Pre-prints, full text, trial registry records of published protocols meeting PICO, abstracts and conference proceedings **	Podcast, editorials, commentary, qualitative design
Study design	• registries- studies using data from databases or hospital/covid • cohort or case control	Any other research design

ICU: intensive care unit; PICO: population, intervention, comparator, outcome framework
*PCR polymerase chain reaction (detection of viral material) or antigen test (detection of viral proteins) test performed on oro- and nasopharyngeal swabs and/or on respiratory-tract secretions and aspirates.
**Abstracts and conference proceedings will be considered if the meet PICO and placed under awaiting classification category.

Measures of effect
Risk ratios, odds ratios and Hazard ratios.

Data extraction (selection and coding)
One researcher will perform title and abstract screening. Two researchers (JB, AF, KB) reviewed the studies in full text, selected studies for inclusion, and extracted and summarised data/results from included studies in tables. A group of experts in the field provided feedback for the study inclusion process, methodological approach, and results presentation.

Risk of Bias assessment

Critical appraisal for data quality will be assessed by one reviewer, using:

- Newcastle Ottawa Scale for either cohort or case control studies.

Strategy for data synthesis
As this work will be conducted at pace, it may only be possible to do a narrative summary.
If times allows and two or more studies are homogenous enough, we will pool the studies. If meta-analysis is possible, we will use a random-effects model to pool data. The I^2 statistic will be used to assess heterogeneity and use the guide as outlined: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% would be considerable heterogeneity (Higgins et al., 2020).

Analysis of subgroups or subsets
If possible, we will explore subgroup analysis based on number of vaccinations, by a world region (Africa/America/Asia/Europe/Oceania), type of population (public/healthcare/patients/pregnant and breastfeed women/parents/students), and gender (male/female).

Project start date: March 18, 2022 - **Project end date:** April 29, 2022

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Appendix 2. Search strategy

Søkelogg: Omikron og risikofaktorer
Søk: Ingrid Harboe
Fagfelle: Elisabet Hafstad

Database	Resultat	Uten dubletter
Cochrane COVID-19 register	126	
Embase	277	
MEDLINE	44	
Totalt	447	392
Avgrensning: 2021-10-01 – 2022-03-17		
Søkedato: 2022-03-17		

Database: Cochrane COVID-19 register

Search: (omicron* or omikron* or "B.1.1.529")
Limit: 2021-10-01 – 2022-03-17
Results: 126

Databases: Embase 1974 to 2022 March 16; Ovid MEDLINE(R) ALL 1946 to March 16, 2022

1	(omicron* or omikron* or "B.1.1.529" or "BA.1" or "BA.1.1" or "BA.2" or "BA.3.").mp.	10959
2	Hospitalization/ or exp Mortality/ or Intensive Care/ or exp Intensive Care Unit/ or exp Artificial Ventilation/ or (hospitalization* or hospitalisation* or hospitalized or hospitalised or ((admit* or admission*) adj3 hospital*) or death* or mortality or ICU or ((intensive or critical) adj3 care) or ventilat* or intubat* or "critical illness" or fatality or "severe illness" or severity or comorbidit* or invasive).mp.	9535528
3	(202110* or 202111* or 202112* or 202201* or 202202* or 202203*).dc.	1235709
4	(omicron* or omikron* or "B.1.1.529" or "BA.1" or "BA.1.1" or "BA.2" or "BA.3.").mp.	10959
5	Hospitalization/ or exp Mortality/ or Intensive Care/ or exp Intensive Care Unit/ or exp Artificial Ventilation/ or (hospitalization* or hospitalisation* or hospitalized or hospitalised or ((admit* or admission*) adj3 hospital*) or death* or mortality or ICU or ((intensive or critical) adj3 care) or ventilat* or intubat* or "critical illness" or fatality or "severe illness" or severity or comorbidit* or invasive).mp.	9535528
6	(202110* or 202111* or 202112* or 202201* or 202202* or 202203*).dt.	695648
7	1 and 2 and 3	286
8	4 and 5 and 6	177
9	7 or 8	463
10	remove duplicates from 9	321
11	10 use oemezd	277
12	10 use medall	44

Appendix 3. Excluded studies and trial registry records

1. Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, et al. Decreased severity of disease during the first global Omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. Int J Infect Dis. 2022;116:38-42.
   a. **Reason:** Wrong comparator
2. Assistance Publique - Hopitaux de P. Impact of SARS-CoV-2 Variability in ICU Hospitalized Patients With Severe Disease. ClinicalTrialsgov. 2021.
   a. Reason: No predictors of severe disease
3. Belay ED, Godfred-Cato S. SARS-CoV-2 spread and hospitalisations in paediatric patients during the Omicron surge. The Lancet Child and Adolescent Health. 2022.
   a. **Reason:** Wrong study design
4. Bhattacharyya RP, Hanage WP. Challenges in Inferring Intrinsic Severity of the SARS-CoV-2 Omicron Variant. N Engl J Med. 2022;386(7) (no pagination).
   a. **Reason:** Wrong study design
5. Birol Ilter P, Prasad S, Berkkan M, Mutlu MA, Tekin AB, Celik E, et al. Clinical severity of SARS-CoV-2 infection among vaccinated and unvaccinated pregnancies during the Omicron wave. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2022;01.
   a. **Reason:** Wrong study design
6. Bouzid D, Visseaux B, Kassasseya C, Daoud A, Femy F, Hermand C, et al. Comparison of Patients Infected With Delta Versus Omicron COVID-19 Variants Presenting to Paris Emergency Departments : A Retrospective Cohort Study. Ann Intern Med. 2022;15:15.
   a. **Reason:** Wrong comparator
7. Christensen PA, Olsen RJ, Long SW, Snehal R, Davis JJ, Saavedra MO, et al. Signals of Significantly Increased Vaccine Breakthrough, Decreased Hospitalization Rates, and Less Severe Disease in Patients with Coronavirus Disease 2019 Caused by the Omicron Variant of Severe Acute Respiratory Syndrome Coronavirus 2 in Houston, Texas. Am J Pathol. 2022;03:03.
   a. **Reason:** Wrong outcomes
8. Cloete J, Kruger A, Masha M, du Plessis NM, Mawela D, Tshukudu M, et al. Rapid rise in paediatric COVID-19 hospitalisations during the early stages of the Omicron wave, Tshwane District, South Africa. medRxiv. 2021;21.
9. Cloete J, Kruger A, Masha M, du Plessis NM, Mawela D, Tshukudu M, et al. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 Omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. The Lancet Child and Adolescent Health. 2022.
   a. **Reason 8&9**: Wrong study design
10. Danza P et al.. SARS-CoV-2 Infection and Hospitalization Among Adults Aged ≥18 Years, by Vaccination Status, Before and During SARS-CoV-2 B.1.1.529 (Omicron) Variant Predominance - Los Angeles County, California, November 7, 2021-January 8, 2022. MMWR Morbidity and mortality weekly report. 2022;71(5):177-81.
    a. **Reason:** No predictors of severe disease
11. Davies MA, Kassanjee R, Rosseau P, Morden E, Johnson L, Solomon W, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection in the Omicron-driven fourth wave compared with previous waves in the Western Cape Province, South Africa. medRxiv. 2022;12.
    a. **Reason:** Wrong comparator
12. Ebell MH, Hamadani R, Kieber-Emmons A. Simple risk scores to predict hospitalization or death in outpatients with COVID-19 including the Omicron variant. medRxiv. 2022;14.
    a. **Reason:** Wrong study design

13. Fall A, Eldesouki RE, Sachithanandham J, Morris CP, Norton JM, Gaston DC, et al. A Quick Displacement of the SARS-CoV-2 variant Delta with Omicron: Unprecedented Spike in COVID-19 Cases Associated with Fewer Admissions and Comparable Upper Respiratory Viral Loads. medRxiv. 2022;28.
    a. **Reason:** Wrong comparator
14. Faroese Hospital S. Long Covid Omicron. ClinicalTrialsgov. 2022.
    a. **Reason:** Wrong patient population
15. Goga A, Bekker LG, Garrett N, Reddy T, Yende-Zuma N, Fairall L, et al. Breakthrough Covid-19 infections during periods of circulating Beta, Delta and Omicron variants of concern, among health care workers in the Sisonke Ad26.COV2.S vaccine trial, South Africa. medRxiv. 2021;21.
    a. **Reason:** Wrong comparator
16. Hussey H, Davies MA, Heekes A, Williamson C, Valley-Omar Z, Hardie D, et al. Assessing the clinical severity of the Omicron variant in the Western Cape Province, South Africa, using the diagnostic PCR proxy marker of RdRp target delay to distinguish between Omicron and Delta infections - a survival analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2022;27.
    a. **Reason:** Wrong comparator
17. Iuliano AD, Brunkard JM, Boehmer TK, Peterson E, Adjei S, Binder AM, et al. Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods - United States, December 2020-January 2022. Mmwr. 2022;Morbidity and mortality weekly report. 71(4):146-52.
    a. **Reason:** Wrong comparator
18. Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California. medRxiv. 2022;11.
    a. **Reason:** Wrong comparator
19. Madhi SA, Kwatra G, Myers JE, Jassat W, Dhar N, Mukendi CK, et al. South African Population Immunity and Severe Covid-19 with Omicron Variant. medRxiv. 2021;21.
    a. **Reason:** Wrong comparator
20. Marks KJ, Whitaker M, Anglin O, Milucky J, Patel K, Pham H, et al. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, July 2021-January 2022. Mmwr. 2022;Morbidity and mortality weekly report. 71(7):271-8.
    a. **Reason:** No predictors of severe disease
21. Martin B, DeWitt PE, Russell S, Sanchez-Pinto LN, Haendel MA, Moffitt R, et al. Acute upper airway disease in children with the Omicron (B.1.1.529) variant of SARS-CoV-2: a report from the National COVID Cohort Collaborative (N3C). medRxiv. 2022;30.
    a. **Reason:** No predictors of severe disease
22. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa during the COVID-19 Omicron Wave Compared with Previous Waves. JAMA - Journal of the American Medical Association. 2022;327(6):583-4.
    a. **Reason:** No predictors of severe disease
23. Mattiuzzi C, Henry BM, Lippi G. COVID-19 vaccination and SARS-CoV-2 Omicron (B.1.1.529) variant: a light at the end of the tunnel? Int J Infect Dis. 2022;09:09.
    a. **Reason:** Wrong comparator
24. Meo SA, Meo AS, Al-Jassir FF, Klonoff DC. Omicron SARS-CoV-2 new variant: Global prevalence and biological and clinical characteristics. European Review for Medical and Pharmacological Sciences. 2021;25(24):8012-8.
    a. **Reason:** Wrong study design

25. Modes ME, Directo MP, Melgar M, Johnson LR, Yang H, Chaudhary P, et al. Clinical Characteristics and Outcomes Among Adults Hospitalized with Laboratory-Confirmed SARS-CoV-2 Infection During Periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) Variant Predominance - One Hospital, California, July 15-September 23, 2021, and December 21, 2021-January 27, 2022. Mmwr. 2022;Morbidity and mortality weekly report. 71(6):217-23.
    a. **Reason:** Wrong comparator
26. Nealon J, Cowling BJ. Omicron severity: milder but not mild. The Lancet. 2022;399(10323):412-3.
    a. **Reason:** Wrong study design
27. Paleker M, Davies MA, Raubenheimer P, Naude J, Boulle A, Hussey H. Change in profile of COVID-19 deaths in the Western Cape during the fourth wave. medRxiv. 2022;12.
    a. **Reason:** No predictors of severe disease
28. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. medRxiv. 2022;16:16.
    a. **Reason**: Wrong comparator
29. Peralta-Santos A, Rodrigues EF, Moreno J, Ricoca V, Casaca P, Fernandes E, et al. Omicron (BA.1) SARS-CoV-2 variant is associated with reduced risk of hospitalization and length of stay compared with Delta (B.1.617.2). medRxiv. 2022;23.
    a. **Reason:** Wrong comparator
30. Robinson ML, Morris CP, Betz J, Zhang Y, Bollinger R, Wang N, et al. Impact of SARS-CoV-2 variants on inpatient clinical outcome. medRxiv. 2022;03:03.
    a. **Reason:** Wrong comparator. Scope of the article does not fit our question
31. Torjesen I. Covid-19: Omicron variant is linked to steep rise in hospital admissions of very young children. BMJ (Clinical research ed). 2022;376:o110.
    a. **Reason:** Wrong study design
32. Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada. medRxiv. 2021;27.
    a. **Reason:** Wrong study design
33. Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 Omicron Variant Severity in Ontario, Canada. JAMA Journal of the American Medical Association. 2022.
    a. **Reason:** Wrong comparator
34. Veneti L, Boas H, Kristoffersen AB, Stalcrantz J, Bragstad K, Hungnes O, et al. Reduced risk of hospitalisation among reported COVID-19 cases infected with the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant, Norway, December 2021 to January 2022. Eurosurveillance. 2022;27(4).
    a. **Reason:** Wrong comparator
35. Vieillard-Baron A, Flicoteaux R, Salmona M, Annane D, Ayed S, Azoulay E, et al. Epidemiological Characteristics and Severity of Omicron Variant Cases in the Aphp Critical Care Units. medRxiv. 2022;28.
    a. **Reason:** Wrong comparator
36. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID infection rates, clinical outcomes, and racial/ethnic and gender disparities before and after Omicron emerged in the US. medRxiv. 2022;22:22.
    a. **Reason:** No predictors of severe disease
37. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. medRxiv. 2022;13.
    a. **Reason:** Wrong comparator
38. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa: a data linkage study. The Lancet. 2022;399(10323):437-46.

a. **Reason:** Wrong study design

Appendix 4. (Excluded) studies of interest

Author	Information of interest
Iuliano 2022 (10) Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods Report	• The study examines age in an in-patient setting i.e., they did not adjust for other risk factors or for difference in the number of infected (un-hospitalised) cases. • The largest relative differences in ED visits and admissions were observed among children and adolescents aged 0–17 years during the Omicron period; however, this age group represented only 14.5% of COVID-19 ED visits and 4.2% of COVID-19 admissions. • Disease severity among hospitalized COVID-19 patients was associated with increasing age; invasive mechanical ventilation and in-hospital deaths were rare among patients aged 0–17 years. • The percentage of hospitalized COVID-19 patients admitted to an ICU during Omicron (13.0%) was 28.8% lower than during the winter 2020–21 (18.2%) and 25.9% lower than during Delta (17.5%) periods overall, and for all three age groups ($p<0.05$) (age groups are 0-17yrs, 18-49yrs and >50yrs). • The percentage of hospitalized COVID-19 patients who received IMV (3.5%) or died while in the hospital (7.1%) during Omicron was lower than during the winter 2020–21 (IMV = 7.5%; deaths = 12.9%) and Delta (IMV = 6.6%; deaths = 12.3%) periods overall, and for both adult age groups ($p<0.001$).
Marks 2022 (11) Hospitalizations of children and adolescents with laboratory confirmed COVID/19 Report	• During December 2021, the monthly hospitalization rate among unvaccinated adolescents aged 12–17 years (23.5) was six times that among fully vaccinated adolescents (3.8) suggesting that vaccines were highly effective in preventing serious COVID-19 illness. • During July 1–December 31, 2021, 42.4% of hospitalized unvaccinated adolescents were non-Hispanic Black adolescents. • A higher proportion of unvaccinated adolescents (70.3%) than fully vaccinated adolescents (40.8%) had COVID-19 as a primary reason for admission. • A significantly higher proportion of unvaccinated adolescents were admitted to the ICU (30.3%) than were those who were vaccinated (15.5%).
Maslo 2022 (12) Characteristics and Outcomes of Hospitalized Patients in South Africa during the COVID-19 Omicron	• A different pattern of characteristics and outcomes in patients hospitalized with COVID-19 was observed in the early phase of the Omicron wave compared with earlier waves in South Africa, with younger patients having fewer comorbidities, fewer hospitalizations and respiratory diagnoses, and a decrease in severity and mortality. • Patients hospitalized during Omicron wave were younger (median age, 36 years vs maximum 59 years in Delta wave; $P < .001$) with a higher proportion of females. • Significantly fewer patients with comorbidities were admitted in Omicron wave,

Wave Compared with Previous Waves Letter	• Of 971 patients admitted in Omicron wave, 24.2% were vaccinated, 66.4% were unvaccinated, and vaccination status was unknown for 9.4%
Modes 2022 (13) Clinical characteristics and outcomes among adults hospitalized with laboratory-confirmed SARS CoV 2 infection during periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) Report – retrospective data from electronic records	• During Omicron predominance, there were no significant differences in ICU admission or invasive mechanical ventilation when stratified by vaccination status. • Fewer fully vaccinated Omicron-period patients died while hospitalized (3.4%), compared with Delta-period patients (10.6%) • Among Omicron-period patients, vaccination was associated with lower likelihood of ICU admission, and among adults aged ≥65 years, lower likelihood of death while hospitalized. • Likelihood of ICU admission and death were lowest among adults who had received a booster dose. • The proportion of fully vaccinated adults who were Hispanic was higher during Omicron predominance (21.9%) than during Delta predominance (10.6%) (p = 0.02). Conversely, non-Hispanic White persons accounted for fewer admissions among fully vaccinated adults during Omicron predominance than during Delta predominance (46.6% versus 62.4%; p = 0.01).
Paredes 2021 (14) Associations between SARS CoV2 variants and risk of COVID 19 hospitalization among confirmed cases in Washington State: a retrospective cohort study Pre-print	• Without stratification by variant lineage, authors found that when compared to the unvaccinated group, cases with a record of an active vaccination but no booster and those with an active booster vaccination both have a lower risk of hospitalization (≥21 days post dose one but <21 days post booster: HR 0.34, 95% CI 0.23-0.50; ≥21 days post booster: HR 0.31 95% CI 0.19 – 0.51) • When stratified by vaccination status, we find progressively lower risks of hospitalization for cases infected with Omicron for those unvaccinated (HR 0.37, 95% CI 0.21- 0.66), vaccinated without a booster (HR 0.23, 95% CI 0.14-0.39), and those ≥21 days post booster (HR 0.19, 95% CI 0.09-0.41), all when compared to unvaccinated cases with Delta infections.
Robinson 2022 (15)	• This study present data of interest, but it is challenging to interpret. The model does not include interaction terms.

Impact of SARS-CoV-2 variants on inpatient clinical outcome. Pre-print	• The 808 patients with history of vaccination or prior COVID-19 included 291 (34%) with Delta and 500 (62%) with Omicron infections; only 17 vaccinated or previously infected patients with Alpha, Ancestral, or other lineages were hospitalized. • There were 67 (23%) vaccinated Delta and 109 (22%) vaccinated Omicron patients who developed severe disease or death within 14 days with median time to event of 0.52 (IQR 0.09-3.15) days. By 14 days of follow up, there remained 43 (5%) vaccinated persons at risk for incident severe disease or death. • Among patients with Omicron and Delta infections, inpatients who were vaccinated or had history of COVID-19 had half the 14-day risk of severe disease or death compared to unvaccinated inpatients (adjusted hazard ratio 0.46, IQR 0.34-0.62).
Wang 2022 (16) COVID infection rates, clinical outcomes, and racial/ethnic and gender disparities before and after Omicron emerged in the US Pre-print – retrospective cohort (electronic records)	• The infection rate was the highest in children under 5 years and reached 11.0 in January 2022, which is 6-9 times of the infection rate during the Delta period between September and November and 3 times of infection rate during the Omicron emergence period in the early December. • Overall infection rates decreased with increasing age. Accordingly, patients over 65 years old had the lowest incidence rate. Infection rates were higher in men than in women for both Delta and Omicron periods though differences were small and remained constant. • Between 26. December 2021 and 20. January.2022, the incidence rate among Black patients was 8.2-14.0, which were 2.9-3.7 times of the rates in White patients (P.<0.001). Significant differences were observed between Hispanic and non-Hispanic patients and the ethnic disparity was widened during the Omicron predominance period. • Significant racial and ethnic disparities in infection rate were consistent across all age groups during the Omicron predominance period (data not shown). • There was significant difference in ED visits in the 3-day time-window after COVID infections between infected Black and White patients after propensity-score matching for age, gender, socioeconomic factors, morbidities, medications, and documented vaccination status. In the Omicron cohort, the rate for ED visits in Black patients was 14.4%, higher than 7.8% in the matched White patients (RR: 1.83 [1.75-1.92]). • Significant difference in ED visits were observed between matched Hispanic and non-Hispanic patients in the Omicron - In the Omicron cohort, the rate for ED visits in Hispanic patients was 25.2%, higher than 12.8% in the matched non-Hispanic patients (RR: 1.98 [1.85-2.11]). • Hospitalization risk did not differ between matched Black and White patients in the Omicron cohort. • No marked difference in hospitalizations was observed between Hispanic and non-Hispanic patients after matching for age, gender, socioeconomic factors, morbidities, medications, and documented vaccination status. • There was significant difference in ICU admissions between matched Black and White patients in the Omicron cohort. The risk for ICU admissions in Black patients was 0.43%, higher than 0.28% in the matched White patients (RR: 1.54 [1.17-2.01]). Similar difference in ICU admissions were observed between matched Hispanic and non-Hispanic

	patients. In the Omicron cohort, the risk for ICU admissions in Hispanic patients was 0.75%, higher than 0.51% in the matched non-Hispanic patients (RR: 1.48 [1.01-2.16]). • Women had lower risks than men for ED visits, hospitalizations, and ICU admissions in the Omicron cohort after matching for race, ethnicity, socioeconomic factors, morbidities, medications, and documented vaccination status. This gender difference was especially profound for ICU admissions. In the Omicron cohort the risk for ICU admissions in women was 0.35%, compared to 0.57% in men (RR: 0.63 [0.54-0.75])

ED: emergency department; HR: hazard ratio; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; RR: Relative risk.

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