



Risk of severe outcomes from COVID-19 in comorbid populations in the Omicron era: A systematic review and meta-analysis

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ABSTRACT

Objectives: This is the first meta-analysis assessing mortality and hospitalization risk from COVID-19 in individuals with comorbidities versus those without during the Omicron era.

Methods: A systematic search (Embase, MEDLINE, PubMed, Europe PMC, Latin American and Caribbean Health Sciences Literature, Cochrane COVID-19 Study Register, WHO COVID-19 Database) identified studies published between January 2022 and March 2024. Studies included people with at least one of the following comorbidities: cardiovascular/cerebrovascular disease, chronic lung conditions, diabetes, and obesity. Studies were synthesized quantitatively using random-effect models. Evaluated outcomes were risk of death, hospitalization, intensive care unit (ICU) admission, and any combination of these outcomes.

Results: Of 72 studies, 68 were meta-analyzed. Participant numbers per comorbidity ranged from 328,870 to 13,720,480. Risks of death, hospitalization, and the combined outcome were increased in individuals with cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, respiratory diseases, heart disease, and heart failure (pooled relative risk [RR] range: 1.27 [heart disease, hospitalization; 95% CI: 1.17–1.38] to 1.78 [heart failure, death; 95% CI: 1.46–2.16]). Diabetes and obesity were associated with increased ICU admission risk (RR: 1.20, 95% CI: 1.04–1.38; RR: 1.32, 95% CI: 1.11–1.57, respectively).

Conclusion: During the Omicron era, individuals with comorbidities faced increased risks of severe outcomes from COVID-19.

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Introduction

At an early stage of the COVID-19 pandemic, individuals with comorbidities, including diabetes, obesity, respiratory, and cardiovascular diseases were more likely to experience adverse health outcomes caused by SARS-CoV-2 infection [1,2]. Such populations

may be at increased risk of death and hospitalization in comparison with the general population [1–4].

Patients infected with SARS-CoV-2 Omicron variants have exhibited milder infections and reduced hospitalization compared with the earlier Delta (B.1.617.2) variant [5–7]. Despite this, Omicron (B.1.1.529) was classified as a variant of concern by the World Health Organization (WHO) in November 2021 due to a detrimental change in COVID-19 epidemiology [8]. In particular, individuals with pre-existing comorbidities may still be at a higher risk of complications and death from SARS-CoV-2 infection in the cur-

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rent Omicron era than individuals in the general population [9]. As SARS-CoV-2 Omicron variants evolve, understanding the impact and risk of infection on individuals with comorbidities is crucial for informed treatment and risk mitigation through vaccination or other preventative measures.

Previous systematic literature reviews (SLRs) have shown an increased risk of severe COVID-19 outcomes in comorbid populations during pre-Omicron COVID-19 periods [10–15]. However, to our knowledge, this is the first SLR and meta-analysis aimed at assessing the risk of mortality and hospitalization from COVID-19 in individuals with comorbidities, including cardiovascular/cerebrovascular diseases, chronic lung conditions, diabetes, and obesity, during the Omicron era.

Methods

The SLR protocol is registered with PROSPERO (CRD42024501163). This SLR and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA).

Search strategy

The following databases were searched: Embase, MEDLINE, PubMed, Europe PMC (including MedRxiv and bioRxiv preprints), Latin American and Caribbean Health Sciences Literature, the Cochrane COVID-19 Study Register, and the WHO COVID-19 Database. Search strategies were structured using terms related to COVID-19 infection, risk, and burden of illness (Supplementary Methods).

Eligibility criteria

Eligible studies included people (all ages) with at least one of the following comorbidities: cardiovascular/cerebrovascular disease, chronic lung conditions, diabetes, and obesity (Supplementary Table 1).

Individuals without the respective comorbidities or the general population were used as the comparator group. Evaluated outcomes were the risks of death, hospitalization (for any reason), intensive care unit (ICU) admission (for any reason), and the combined outcome (any combination of the other outcomes). COVID-19 outcomes were determined by including studies where either all patients had COVID-19 at the start of the study or all deaths and hospitalizations were related to COVID-19 (defined by the studies).

Included studies were observational (cohort, case-control, cross-sectional), published between 1 January 2022 and 13 March 2024, with full texts published in English.

Study selection, data extraction, and quality assessment

Identified studies were first assessed at title and abstract level by two independent reviewers to determine whether inclusion criteria were met, followed by full text screening of all studies found to be eligible. For details of data extraction and quality assessment, see Supplementary Methods.

Data synthesis and analysis

Qualitative data synthesis

All studies included in the review were assessed qualitatively to identify which studies could be combined in a meta-analysis (Supplementary Methods). Comorbidities were grouped as follows, based on recommendations from clinical experts: asthma, cerebrovascular disease, chronic obstructive pulmonary disease (COPD),

diabetes, obesity, peripheral vascular disease (PVD), respiratory diseases (excluding asthma and COPD), atrial fibrillation, heart disease, heart failure, hypertension, and thrombosis.

Statistical analysis

For the primary analyses, pairwise meta-analyses were performed for the risks of death, hospitalization, ICU admission, and the combined outcome for the comorbid populations, using the most adjusted reported outcome estimates. The robustness of the results was assessed using “Leave-1-out,” “Least adjusted,” “Only adjusted,” and “Excluding studies for population overlap” sensitivity analyses.

Subgroup analyses were conducted for the ‘Hospitalized’ or ‘General’ populations, which included only individuals who were or were not already hospitalized when they started the study, respectively. Additional subgroup analyses were performed for the ‘> 50 years’ population, which included only participants older than 50 years, and the “COVID-19-related outcomes only” population, which included only outcomes explicitly caused by COVID-19 (Supplementary Methods).

All statistical analyses were performed in R version 4.1.1 (R Foundation for Statistical Computing) using the meta package. A statistically significant ($p < 0.05$) result is referred to as significant thereafter.

Results

In total, 21,937 records were identified through searches and one study was identified via reference checking. Following elimination of duplicates, 11,593 remaining studies underwent title and abstract screening of which 3123 studies were assessed in full text screening. A total of 72 studies were selected for inclusion (Figure 1).

Study characteristics

Study characteristics are summarized in Supplementary Table 2. The studies were performed in 26 different countries, primarily in Europe ($n = 15$), China ($n = 14$), and the USA ($n = 13$). Most studies were retrospective cohort studies ($n = 58$), followed by prospective cohort ($n = 7$), cross-sectional ($n = 6$), and case-control ($n = 1$) studies. The “Death,” “Hospitalization,” “ICU admission,” and “Combined” outcomes were reported in 45, 17, 20, and 17 studies, respectively. Most studies did not report Omicron subvariants, but in studies that did, BA.1 was the most common. Other reported subvariants included BA.2, BA.4, BA.5, BF.7, BQ.1, and XXB. Supplementary Table 3 provides visualization of the Omicron period in the included studies.

Patient characteristics

Patient characteristics are summarized in Supplementary Table 4. Minimum numbers of participants included in analyses for each comorbidity across the included studies are reported in Table 1. Most studies ($n = 42$) included a ‘Hospitalized Population’, and the rest ($n = 30$) included ‘General Population’. These populations included individuals who were and were not hospitalized at the start of the study, respectively (Supplementary Table 4). Diabetes was the most commonly reported comorbidity ($n = 50$ studies; Table 1) and thrombosis the least commonly reported ($n = 4$ studies). The majority of studies ($> 50\%$) that reported vaccination status included fully vaccinated individuals.

Risk of bias assessment

Risk of bias (Supplementary Table 5) was assessed in all included studies ($n = 72$); 56 and 14 were found to be low and

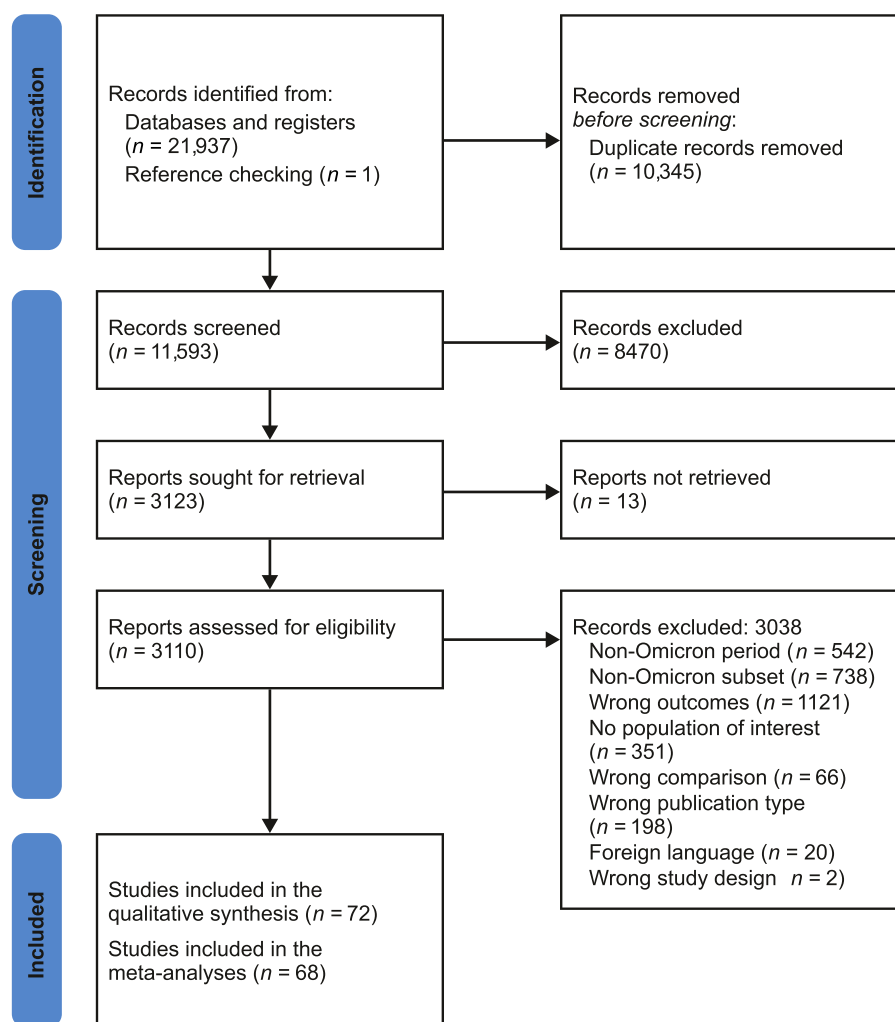


Figure 1. PRISMA flow diagram.

medium risk, respectively. Two studies [16,17] were found to be high risk and were excluded from the analysis. Two additional studies were excluded from the analysis for not reporting confidence intervals ($n = 1$) [18] and for conflicting interpretation of results within the study ($n = 1$) [19].

Meta-analysis

The relative risk (RR) for death, hospitalization, ICU admission, and combined outcomes among individuals with each comorbidity compared with individuals without comorbidities are shown in Figure 2.

Due to insufficient numbers of studies, meta-analysis was not conducted for the following outcomes and comorbid conditions: ICU admission for asthma, cerebrovascular diseases, COPD, and heart failure; all outcomes except the combined outcome for atrial fibrillation; and all outcomes for PVD and thrombosis (Table 1). These outcomes and comorbidities are excluded from the following meta-analysis but synthesized narratively in the supplement (Supplementary Results: Section 2.4).

Risk of death

Individuals with any of the comorbidities meta-analyzed, except asthma and obesity, had a significantly increased risk of

death compared with individuals without the respective comorbidity (Figure 2a, Supplementary Table 6).

Statistical heterogeneity was considerable in all analyses except among the comorbid populations with heart failure and hypertension, which had substantial heterogeneity (Figure 2a). There was no statistical evidence of publication bias for any of the applicable comorbid populations analyzed, except diabetes (Supplementary Table 7).

All sensitivity analyses results had the same direction of effect and degree of significance as the main analysis for the risk of death outcome (Supplementary Table 7), indicating robustness of the main analysis results.

Subgroup analyses showed the direction of effect, versus the main analysis, changed for individuals with asthma in the 'Hospitalized' and '> 50 years' subgroups (i.e., these groups with asthma had a significantly lower risk of death versus those without asthma) (Supplementary Table 8).

Risk of hospitalization

For all meta-analyzed comorbid conditions, except asthma, individuals with the comorbidity had a significantly increased risk of hospitalization in comparison with individuals without the comorbidity (Figure 2b, Supplementary Table 6). Statistical heterogeneity was substantial or considerable for most comorbidities (7/9 applicable comorbid populations; Figure 2b). Publication bias was not

Table 1

Number of studies, subgroups, and minimum number of participants included in each comorbidity population analysis.

Comorbidity	Number of studies reporting comorbidity	Number of studies included in 'Main' meta-analysis	Number of subgroups ^a included in each 'Main' comorbidity population analysis by outcome				Minimum number of participants included in each comorbidity population analysis ^c
			Death	Hospitalization	ICU admission	Combined	
Diabetes	50	47	40	13	13	19	6,740,188
Heart disease	39	37	29	8	11	17	4,994,559
Hypertension	38	35	23	5	7	17	13,720,480
Respiratory diseases	30	28	23	6	7	10	1,798,041
Obesity	28	22	21	9	6	7	8,186,661
Asthma	23	20	12	5	3 ^b	9	10,348,017
COPD	21	20	12	8	3 ^b	9	1,466,035
Cerebrovascular diseases	20	17	11	6	3 ^b	8	2,071,755
Heart failure	17	16	11	7	3 ^b	7	821,376
Atrial fibrillation	10	5	4 ^b	4 ^b	2 ^b	5	1,507,834
PVD	5	0	3 ^b	2 ^b	0 ^b	3 ^b	344,177
Thrombosis	4	0	3 ^b	2 ^b	0 ^b	2 ^b	328,870

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PVD, peripheral vascular disease.

^aSubgroups distinguish between the comorbidities of interest and may contain additional information that differentiates the comorbidity from another one included in the same meta-analysis by the same study (e.g., "men with stroke" and "women with stroke"). Some studies reported multiple subgroups that are included in the same meta-analysis.^bMeta-analyses were not conducted for analyses with fewer than five subgroups.^cBreakdown of numbers of participants by outcome not provided as most studies included more than one outcome of interest.

Darker green indicates greater number of studies, subgroups, or participants.

assessed in any of the analyses due to the small number of studies, except in the comorbid group with diabetes, where no bias was found (Supplementary Table 9).

All sensitivity analyses results had the same direction of effect, and nearly all had the same degree of significance, as the main analyses for the risk of hospitalization outcome (Supplementary Table 9), indicating robustness of the main analysis results.

In all subgroup analyses, the direction of effect was the same compared with the main analysis, except individuals with asthma had a (non-significantly) lower risk of hospitalization. In nearly all analyses the significance level remained unchanged (Supplementary Table 10).

Risk of ICU admission

While all five meta-analyzed comorbidities had an increased risk of ICU admission compared with individuals without the comorbidity, this risk was significant in diabetes and obesity only (Figure 2c, Supplementary Table 6).

Statistical heterogeneity ranged from not important to considerable across the analyses. Publication bias was not assessed in any of the analyses due to the small number of studies, except in the groups with diabetes and heart disease, in which no bias was found (Supplementary Table 11).

Four sensitivity analyses resulted in loss or gain of significance compared with the main analysis for risk of admission to ICU, although the direction of effect (i.e., the higher risk of ICU admission) remained the same (Supplementary Table 11).

In the "COVID-19-related outcomes only" subgroup, the increased risk of ICU admission for comorbid populations with respiratory diseases and heart disease was significant (Supplementary Table 12), while this relationship was non-significant in the main analysis.

Risk of the combined outcome (death, hospitalization, or ICU admission)

For all comorbid conditions, individuals with the comorbidity had a significantly increased risk of the combined outcome in comparison with individuals without the comorbidity, except in individuals with asthma and hypertension, where the increased risk was non-significant, and in individuals with obesity, who had a lower (but non-significant) risk of the combined outcome in comparison with individuals without obesity (Figure 2d, Supplementary Table 6). For details of sensitivity and subgroup analyses for the combined outcome see Supplementary Results and Supplementary Tables 13 and 14.

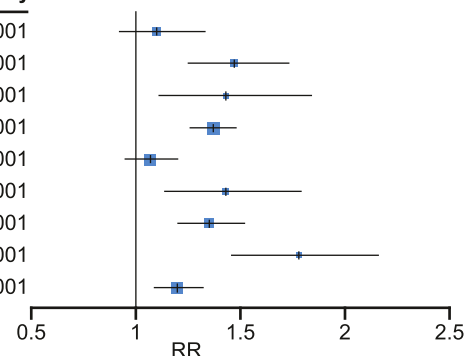
Individual meta-analyses for each comorbidity, stratified by outcome, can be found in the supplement (Supplementary Results: Section 2.4).

Discussion

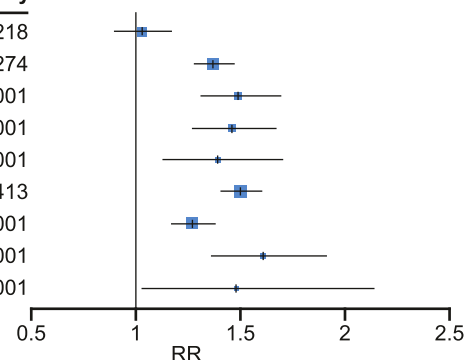
This SLR and meta-analysis examined the impact of SARS-CoV-2 on four outcomes in populations with comorbidities versus those without during the Omicron era. For those with cerebrovascular disease, COPD, diabetes, respiratory diseases (excluding COPD and asthma), heart disease, and heart failure, the pooled RRs of death, hospitalization, and a combined outcome were significantly higher, ranging from 1.27 (95% confidence interval [CI]: 1.17-1.38) to 1.78 (95% CI: 1.46-2.16). Individuals with hypertension had a significantly increased risk of death and hospitalization, with pooled RRs of 1.20 (95% CI: 1.09-1.32) and 1.48 (95% CI: 1.03-2.14), respectively. Those with obesity and atrial fibrillation demonstrated a significantly increased risk of hospitalization and combined outcomes, respectively, with pooled RRs of 1.39 (95% CI: 1.13-1.70) and 1.59 (95% CI: 1.34-1.90). Additionally, individuals with diabetes and obesity had a significantly increased risk of ICU admission, with

a: Death

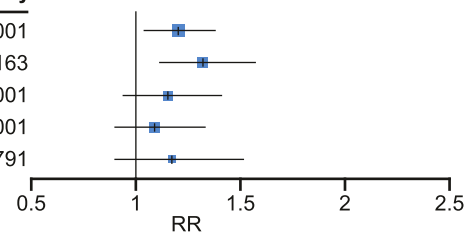
Comorbidity	RR (95% CI)	<i>p</i> value	No. of subgroups	Heterogeneity
Asthma	1.1 (0.92, 1.33)	0.302	12	93%, $p < 0.001$
Cerebrovascular	1.47 (1.25, 1.73)	< 0.001	11	90%, $p < 0.001$
COPD	1.43 (1.11, 1.84)	0.00498	12	94%, $p < 0.001$
Diabetes	1.37 (1.26, 1.48)	< 0.001	40	91%, $p < 0.001$
Obesity	1.07 (0.95, 1.2)	0.268	21	92%, $p < 0.001$
Respiratory diseases	1.43 (1.14, 1.79)	0.00174	23	98%, $p < 0.001$
Heart disease	1.35 (1.2, 1.52)	< 0.001	29	98%, $p < 0.001$
Heart failure	1.78 (1.46, 2.16)	< 0.001	11	87%, $p < 0.001$
Hypertension	1.2 (1.09, 1.32)	< 0.001	23	78%, $p < 0.001$

**b: Hospitalization**

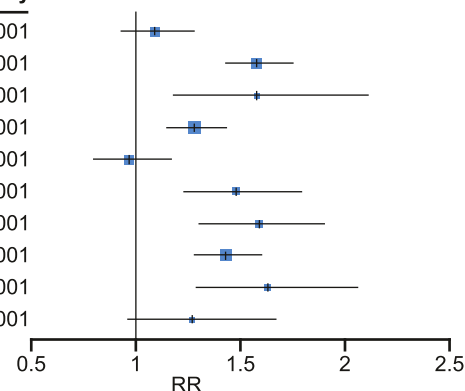
Comorbidity	RR (95% CI)	<i>p</i> value	No. of subgroups	Heterogeneity
Asthma	1.03 (0.9, 1.17)	0.693	5	65%, $p = 0.0218$
Cerebrovascular	1.37 (1.28, 1.47)	< 0.001	6	21%, $p = 0.274$
COPD	1.49 (1.31, 1.69)	< 0.001	8	91%, $p < 0.001$
Diabetes	1.46 (1.27, 1.67)	< 0.001	13	96%, $p < 0.001$
Obesity	1.39 (1.13, 1.7)	0.00158	9	89%, $p < 0.001$
Respiratory diseases	1.5 (1.41, 1.6)	< 0.001	6	0%, $p = 0.413$
Heart disease	1.27 (1.17, 1.38)	< 0.001	8	74%, $p < 0.001$
Heart failure	1.61 (1.36, 1.91)	< 0.001	7	91%, $p < 0.001$
Hypertension	1.48 (1.03, 2.14)	0.0341	5	90%, $p < 0.001$

**c: ICU Admission**

Comorbidity	RR (95% CI)	<i>p</i> value	No. of subgroups	Heterogeneity
Diabetes	1.2 (1.04, 1.38)	0.0141	13	72%, $p < 0.001$
Obesity	1.32 (1.11, 1.57)	0.00158	6	37%, $p = 0.163$
Respiratory diseases	1.15 (0.94, 1.41)	0.162	7	84%, $p < 0.001$
Heart disease	1.09 (0.9, 1.33)	0.37	11	94%, $p < 0.001$
Hypertension	1.17 (0.9, 1.51)	0.235	7	0%, $p = 0.791$

**d: Combined Outcome**

Comorbidity	RR (95% CI)	<i>p</i> value	No. of subgroups	Heterogeneity
Asthma	1.09 (0.93, 1.28)	0.291	9	93%, $p < 0.001$
Cerebrovascular	1.58 (1.43, 1.75)	< 0.001	8	84%, $p < 0.001$
COPD	1.58 (1.18, 2.11)	0.00229	9	99%, $p < 0.001$
Diabetes	1.28 (1.15, 1.43)	< 0.001	19	84%, $p < 0.001$
Obesity	0.97 (0.8, 1.17)	0.714	7	84%, $p < 0.001$
Respiratory diseases	1.48 (1.23, 1.79)	< 0.001	10	78%, $p < 0.001$
Atrial fibrillation	1.59 (1.34, 1.9)	< 0.001	5	91%, $p < 0.001$
Heart disease	1.43 (1.28, 1.6)	< 0.001	17	92%, $p < 0.001$
Heart failure	1.63 (1.29, 2.06)	< 0.001	7	98%, $p < 0.001$
Hypertension	1.27 (0.96, 1.67)	0.0945	17	98%, $p < 0.001$

**Figure 2.** Forest plots of the risk of (a) death, (b) hospitalization, (c) ICU admission, and (d) combined outcome by comorbid population.

pooled RRs of 1.20 (95% CI: 1.04–1.38) and 1.32 (95% CI: 1.11–1.57), respectively.

Of the meta-analyzed comorbid populations, individuals with heart failure had the greatest increase in pooled RRs of death at 1.78 (95% CI: 1.46–2.16), hospitalization at 1.61 (95% CI: 1.36–1.91), and the combined outcome at 1.63 (95% CI: 1.29–2.06). Individuals with asthma had a non-significant increase in risk of any severe outcome, but hospitalized individuals with asthma had a significantly lower pooled RR of death at 0.84 (95% CI: 0.75–0.95) compared with hospitalized individuals without asthma.

Cardiovascular and cerebrovascular disease

Individuals with cerebrovascular disease, heart disease, and heart failure had a significantly higher risk of all severe outcomes from COVID-19, except ICU admission. This is consistent with several studies conducted prior to and during the Omicron era which reported longer time to recovery [20] and a greater risk of severe outcomes from COVID-19 in patients with cerebrovascular [21–24] and cardiovascular diseases [10,22–24]. In the current study, individuals with hypertension had a significantly higher risk of death and hospitalization, but not ICU admission or combined outcomes, consistent with a pre-Omicron meta-analysis [11], although this previous study also reported a significantly higher risk of ICU admission. Individuals with atrial fibrillation had a significantly higher risk of the combined outcome.

The underlying mechanisms for these outcomes are not well understood, but several have been proposed. For cerebrovascular disease, proinflammatory and hypercoagulable states associated with COVID-19 have been suggested [25,26]. For heart disease, possible mechanisms include COVID-19-associated hypercoagulation, direct viral damage to cardiomyocytes, or pneumonia-induced gas exchange obstruction leading to cardiomyocyte injury and apoptosis [2,10]. In heart failure and hypertension, viral uptake through increased angiotensin-converting enzyme 2 (ACE2) receptors may increase the risk of severe outcomes [11,27]. Direct cardiac injury, increased coagulation abnormalities, thrombotic events, and stress cardiomyopathy increase the risk of severe outcomes in individuals with heart failure or atrial fibrillation [27,28].

Respiratory diseases

Individuals with COPD and other respiratory diseases (including acute respiratory distress syndrome, interstitial lung disease, and chronic lung diseases excluding asthma), had significantly higher risks of death, hospitalization, and the combined outcome, consistent with a pre-Omicron meta-analysis on COPD [12].

Micro-thrombosis, secondary bacterial infection, and the effects of intrapulmonary shunting, have been proposed as potential mechanisms increasing the risk of severe outcomes from COVID-19 in COPD [29]. For all chronic respiratory diseases, reduced lung function at baseline may decrease tolerance to further lung injury from SARS-CoV-2 infection, resulting in poorer outcomes [30]. Additionally, individuals with chronic lung disease may experience impaired responses to vaccines, which may lead to an increased risk of acquiring SARS-CoV-2 and developing severe complications [31].

The lack of association between asthma and severe outcomes from COVID-19 may be attributed to down-regulated ACE2 receptors in those with T2-high asthma, reducing susceptibility to SARS-CoV-2 infection [32]. A previous meta-analysis found a similar protective effect of asthma; it is possible that controlling asthma symptoms by routine asthma treatment reduces worsening of symptoms and risk of hospitalization [33].

Diabetes

Risk of severe outcomes from COVID-19 was significantly increased in individuals with diabetes, consistent with pre-Omicron studies that reported an increased risk of mortality [13,23]. Cytokine storm, pulmonary and endothelial dysfunction, and hypercoagulation have been attributed as potential mechanisms increasing the risk of severe outcomes [34].

Obesity

Risk of ICU admission and hospitalization were significantly increased in individuals with obesity, but there was no association with death and the combined outcome. A pre-Omicron SLR and meta-analysis found a similar pattern, with an increased risk of COVID-19-related hospitalizations, but also death, unlike the current study [14]. The increased risk of severe disease may be explained by a hyperinflammatory response to SARS-CoV-2 infection linked to high blood levels of saturated fatty acids in patients with obesity [35], as well as predisposition to immunopathological exaggeration of immuno-metabolic disorders [36]. A possible explanation for the protective effect from death observed in our study is that where ICU occupancy was reaching capacity within a hospital trust, individuals with obesity were explicitly prioritized in ICU admission decisions. This prioritization could be due to the difficulty in maintaining adequate oxygen levels without mechanical ventilation on a normal hospital ward [37]. Consequently, they may have received higher standard of care [37].

Quality of evidence

To our knowledge, this is the first comprehensive SLR to assess severe outcomes from COVID-19 in people with comorbidities during the Omicron era. Most of the results included in the meta-analyses were adjusted for age, comorbidities, and vaccination status, and main analyses were based on these most adjusted estimates, thereby increasing confidence in the findings and likely yielding conservative pooled estimates. In addition, several sensitivity and subgroup analyses were performed, and most sensitivity analyses showed no change in significance from the main analyses, indicating that the pooled estimates are robust.

This study had several limitations. First, there was high clinical and statistical heterogeneity between the studies, due, in part, to variation in interpretation of outcome definitions. This was especially pronounced for the combined outcome as multiple different outcomes were included in its definition. In addition, different adjustments were used between studies: while most studies were adjusted for demographic characteristics, there were variations in adjustments of vaccination rate and comorbidities, reducing comparability of the studies.

Second, while studies included in this review cover wide geographical areas, inter-country differences, such as country-level income, are important predictors of COVID-19 control measures, which in turn affect COVID-19 rates and severity [38,39]. However, analysis by geographical region was not performed due to the high between-study heterogeneity and small numbers of studies by region. Finally, due to lack of data, high between-study heterogeneity, and overlap in Omicron subvariant time periods, no sub-analyses were performed by time period, subvariant, vaccine type, or vaccination status. These can be important effect modifiers and should be investigated in future research.

Implications for practice and further research

This study synthesizes data to enhance healthcare providers' understanding of COVID-19 disease burden in populations with co-

morbidities during the Omicron era and ensure targeted measures are implemented.

Vaccination is the most effective tool to reduce the risk and prevalence of COVID-19 disease, COVID-19-related hospitalization, ICU admission, and death [4,40]. Targeting vaccination and other public health measures for those patients at greatest risk due to comorbidity may help prevent or mitigate severe outcomes from COVID-19.

Due to lack of data for several comorbidities in the Omicron era, further high-quality prospective studies are needed to investigate severe outcomes from COVID-19 in the following populations: type 1 and type 2 diabetes, PVD, hypertension, and thrombosis. It would be valuable to investigate the effects of multi-morbidity and the severity of comorbidities on patient outcomes, as well as the reciprocal effect of COVID-19 on the underlying comorbidities.

Finally, further investigations into the impact of age, evolving variants, vaccination status, and geographical region on comorbid individuals with COVID-19 in the Omicron era, are likely to provide more insight into disease epidemiology.

Conclusions

This SLR and meta-analysis on the burden of COVID-19 in individuals with comorbidities during the Omicron era demonstrated that those with cerebrovascular disease, COPD, diabetes, respiratory diseases, heart disease, heart failure, and hypertension are at increased risk of death and hospitalization, while individuals with diabetes and obesity are at increased risk of ICU admission, in comparison with those without the respective comorbidity. Of the meta-analyzed comorbid conditions, heart failure was associated with the greatest increase in risk of severe outcomes from COVID-19. Clinicians and policy makers should consider targeting public health measures, such as seasonal vaccination, and antiviral therapy in SARS-CoV-2 positive individuals, toward these most at-risk groups to protect vulnerable populations with comorbidities who are at higher risk for developing severe outcomes following COVID-19 disease.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sultan Abduljawad is an employee of BioNTech UK Ltd. Dan H. Barouch has no conflicts of interest. Akvile Chapman is an employee of Maverex Ltd., which received consulting fees from BioNTech SE.

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CRediT authorship contribution statement

Akvile Chapman: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Dan H. Barouch:** Writing – original draft, Writing – review & editing. **Gregory Y.H. Lip:** Writing – original draft, Writing – review & editing. **Triantafyllos Pliakas:** Validation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Eva Polverino:** Writing – original draft, Writing –

review & editing. **Harald Sourij:** Conceptualization, Writing – original draft, Writing – review & editing. **Sultan Abduljawad:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Ethics statement

Ethical approval was not required for this study as it did not involve the use of human or animal subjects.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2025.107958](https://doi.org/10.1016/j.ijid.2025.107958).

References

- [1] Nab L, Parker EPK, Andrews CD, Hulme WJ, Fisher L, Morley J, et al. Changes in COVID-19-related mortality across key demographic and clinical subgroups in England from 2020 to 2022: a retrospective cohort study using the OpenSAFELY platform. *Lancet Public Health* 2023;8 e364–e77. doi:10.1016/S2468-2667(23)00079-8.
- [2] Harrison SL, Buckley BJR, Rivera-Caravaca JM, Zhang J, Lip GYH. Cardiovascular risk factors, cardiovascular disease, and COVID-19: an umbrella review of systematic reviews. *Eur Heart J Qual Care Clin Outcomes* 2021;7:330–9. doi:10.1093/ehjqcco/qcab029.
- [3] Chatterjee S, Nalla LV, Sharma M, Sharma N, Singh AA, Malim FM, et al. Association of COVID-19 with comorbidities: an update. *ACS Pharmacol Transl Sci* 2023;6:334–54. doi:10.1021/acspsci.2c00181.

- [4] Ellis RJ, Moffatt CR, Aaron LT, Beaverson G, Chaw K, Curtis C, et al. Factors associated with hospitalisations and deaths of residential aged care residents with COVID-19 during the Omicron (BA.1) wave in Queensland. *Med J Aust* 2023;**218**:174–9. doi:10.5694/mja2.51813.
- [5] Veneti L, Bøås H, Bråthen Kristoffersen A, 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. *Euro Surveill* 2022;**27**:2200077. doi:10.2807/1560-7917.ES.2022.27.4.2200077.
- [6] 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* 2022;**327**:583–4. doi:10.1001/jama.2021.24868.
- [7] Sheikh A, Kerr S, Woolhouse M, McMenamin J, Robertson CEAVE II Collaborators. Severity of omicron variant of concern and effectiveness of vaccine boosters against symptomatic disease in Scotland (EAVE II): a national cohort study with nested test-negative design. *Lancet Infect Dis* 2022;**22**:959–66. doi:10.1016/S1473-3099(22)00141-4.
- [8] World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern; 2021 [https://www.who.int/news/item/26-11-2021-classification-of-omicron-\(b.1.1.529\)-sars-cov-2-variant-of-concern](https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern) [accessed July 3 2021].
- [9] Jose MM, Feng J, Nguyen HT, Juneau C, Manakatt BM, Barnett J, et al. The influence of comorbidities, general health status, and self-care self-efficacy on COVID-19 symptoms during the omicron wave. *Cureus* 2023;**15**:e49176. doi:10.7759/cureus.49176.
- [10] Mishra P, Parveen R, Bajpai R, Samim M, Agarwal NB. Impact of cardiovascular diseases on severity of COVID-19 patients: a systematic review. *Ann Acad Med Singap* 2021;**50**:52–60. doi:10.47102/annals-acadmedsg.2020367.
- [11] Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst* 2020;**21**:1470320320926899. doi:10.1177/1470320320926899.
- [12] Gerayeli FV, Milne S, Cheung C, Li X, Yang CWT, Tam A, et al. COPD and the risk of poor outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 2021;**33**:100789. doi:10.1016/j.eclinm.2021.100789.
- [13] Javid FA, Waheed FA, Zainab N, Khan H, Amin I, Bham A, et al. COVID-19 and diabetes in 2020: a systematic review. *J Pharm Policy Pract* 2023;**16**:42. doi:10.1186/s40545-023-00546-z.
- [14] Sawadogo W, Tsegaye M, Gizaw A, Adera T. Overweight and obesity as risk factors for COVID-19-associated hospitalisations and death: systematic review and meta-analysis. *BMJ Nutr Prev Health* 2022;**5**:10–18. doi:10.1136/bmjnp-2021-000375.
- [15] Zhou Y, Yang Q, Chi J, Dong B, Lv W, Shen L, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. *Int J Infect Dis* 2020;**99**:47–56. doi:10.1016/j.ijid.2020.07.029.
- [16] Geng Y, Nie Q, Liu F, Pei Y, Chen Q, Zhang H, et al. Understanding clinical characteristics influencing adverse outcomes of Omicron infection: a retrospective study with propensity score matching from a Fangcang hospital. *Front Cell Infect Microbiol* 2023;**13**:1115089. doi:10.3389/fcimb.2023.1115089.
- [17] Shakor A S A A, Samsudin EZ, Chen XW, Ghazali MH. Factors associated with COVID-19 brought-in deaths: a data-linkage comparative cross-sectional study. *J Infect Public Health* 2023;**16**:2068–78. doi:10.1016/j.jiph.2023.10.016.
- [18] Morris CP, Eldesouki RE, Sachithanandham J, Fall A, Norton JM, Abdullah O, et al. Omicron subvariants: clinical, laboratory, and cell culture characterization. *Clin Infect Dis* 2023;**76**:1276–84. doi:10.1093/cid/ciac885.
- [19] Bao S, Lu G, Kang Y, Zhou Y, Wang Y, Yan L, et al. A diagnostic model for serious COVID-19 infection among older adults in Shanghai during the Omicron wave. *Front Med (Lausanne)* 2022;**9**:1018516. doi:10.3389/fmed.2022.1018516.
- [20] Oelsner EC, Sun Y, Balte PP, Allen NB, Andrews H, Carson A, et al. Epidemiologic features of recovery from SARS-CoV-2 infection. *JAMA Netw Open* 2024;**7**:e2417440. doi:10.1001/jamanetworkopen.2024.17440.
- [21] Ferrone SR, Sanmartin MX, Ohara J, Jimenez JC, Feizullayeva C, Lodato Z, et al. Acute ischemic stroke outcomes in patients with COVID-19: a systematic review and meta-analysis. *J Neurointerv Surg* 2024;**16**:333–41. doi:10.1136/jnis-2023-020489.
- [22] Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest* 2020;**158**:97–105. doi:10.1016/j.chest.2020.04.010.
- [23] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–6. doi:10.1038/s41586-020-2521-4.
- [24] Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020;**80**:639–45. doi:10.1016/j.jinf.2020.03.019.
- [25] Katz JM, Libman RB, Wang JJ, Sanelli P, Filippi CG, Gribko M, et al. Cerebrovascular complications of COVID-19. *Stroke* 2020;**51**:e227–e31. doi:10.1161/strokeaha.120.031265.
- [26] Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the global COVID-19 stroke registry. *Stroke* 2020;**51**:e254–e8. doi:10.1161/strokeaha.120.031208.
- [27] Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. *Heart Fail Rev* 2021;**26**:1–10. doi:10.1007/s10741-020-10008-2.
- [28] Li Z, Shao W, Zhang J, Ma J, Huang S, Yu P, et al. Prevalence of atrial fibrillation and associated mortality among hospitalized patients with COVID-19: a systematic review and meta-analysis. *Front Cardiovasc Med* 2021;**8**:720129. doi:10.3389/fcvm.2021.720129.
- [29] Singh D, Mathioudakis AG, Higham A. Chronic obstructive pulmonary disease and COVID-19: interrelationships. *Curr Opin Pulm Med* 2022;**28**:76–83. doi:10.1097/mcp.0000000000000834.
- [30] Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. *Nat Med* 2023;**29**:334–43. doi:10.1038/s41591-022-02156-9.
- [31] Liu H, Aviszus K, Zelarney P, Liao SY, Gerber AN, Make B, et al. Vaccine-elicited B- and T-cell immunity to SARS-CoV-2 is impaired in chronic lung disease patients. *ERJ Open Res* 2023;**9**:00400–2023. doi:10.1183/23120541.00400-2023.
- [32] Sunjaya AP, Allida SM, Di Tanna GL, Jenkins C. Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: systematic review and meta-analysis. *J Asthma* 2022;**59**:866–79. doi:10.1080/02770903.2021.1888116.
- [33] Shi L, Han X, Wang Y, Xu J, Yang H. Significant association between asthma and a lower risk of mortality among COVID-19 patients in Spain: a meta-analysis. *Qatar Med J* 2024;**2024**:34. doi:10.5339/qmj.2024.34.
- [34] Eren S. Diabetes, infection risk and COVID-19. *Mol Metab* 2020;**39**:101044. doi:10.1016/j.molmet.2020.101044.
- [35] Moraes-Vieira P. Immuno-metabolic regulation of macrophages in health and diseases. *FAPESP Week*. São Paulo, Brazil: Fundação de Amparo à Pesquisa do Estado de São Paulo; 2024 <https://fapesp.br/week/study-reveals-new-factor-associated-with-the-risk-of-severe-covid-19-in-people-with-obesity> [accessed July 9, 2025].
- [36] Khwatenge CN, Pate M, Miller LC, Sang Y. Immunometabolic dysregulation at the intersection of obesity and COVID-19. *Front Immunol* 2021;**12**:732913. doi:10.3389/fimmu.2021.732913.
- [37] Dana R, Bannay A, Bourst P, Ziegler C, Losser MR, Gibot S, et al. Obesity and mortality in critically ill COVID-19 patients with respiratory failure. *Int J Obes (Lond)* 2021;**45**:2028–37. doi:10.1038/s41366-021-00872-9.
- [38] Durmuş V. Is the country-level income an important factor to consider for COVID-19 control? An analysis of selected 100 countries. *Int J Health Gov* 2021;**26**:100–13. doi:10.1108/IJHG-10-2020-0121.
- [39] Hopman J, Mehtar S. Country level analysis of COVID-19 policies. *EClinicalMedicine* 2020;**25**:100500. doi:10.1016/j.eclinm.2020.100500.
- [40] Whitaker HJ, Tsang RSM, Byford R, Aspden C, Button E, Sebastian Pillai P, et al. COVID-19 vaccine effectiveness against hospitalisation and death of people in clinical risk groups during the Delta variant period: English primary care network cohort study. *J Infect* 2023;**87**:315–27. doi:10.1016/j.jinf.2023.08.005.