Scientific Advisory Group

COVID-19 Scientific Advisory Group Rapid Evidence Report

Risk Factors for Severe COVID-19 Outcomes

Updated November 19, 2021

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Lay Summary

- This review is an update of a SAG review conducted in August 2020.The purpose of this review is to help doctors, decision-makers, and others identify who is at the highest risk of requiring hospitalization, intensive care, or death from COVID-19.
- Within the inclusion and exclusion criteria for this review, no studies were identified that discussed the relevant risk factors for people who have been vaccinated, COVID-19 variants, or an individual's socioeconomic status and/or race/ethnicity.
- Characterizing a patient's risk of severe disease and understanding the results of studies on individual therapies can inform prioritization decisions to focus treatment of emerging or limited availability therapies on patients most likely to benefit by maximizing clinical benefit, enhancing cost-effectiveness and improving system sustainability.

KEY FINDINGS

- Age and vaccination status have the most impact on whether an individual will get very sick from COVID-19. Risk increases quickly in people who are over 40 years old, and age makes the effect of other conditions even stronger.
- Conditions that clearly increase the risk of severe illness include: Heart disease (including high blood pressure), chronic kidney disease, pregnancy, obesity, stroke, diabetes and chronic obstructive pulmonary disease.
- Being male, having asthma, or smoking were not clearly identified as increasing the risk of severe COVID-19.

RECOMMENDATIONS

- The findings from the first version of this review are still generally accurate. This version solidifies some of the results that were unclear from the first version.
- Three levels of individual factors should be considered for determining risk of severe illness. These are shown in Figure 1 in the practical considerations of this report.
    - Vaccination status is the most important factor. Unvaccinated individuals should be considered high risk, particularly those over the age of 50. Vaccine effectiveness may vary depending on age and other health factors and wanes over time.
    - Age is a powerful predictor of severe illness. Risk increases with age, particularly in unvaccinated patients.
    - Other health conditions make up the third level of risk. High-risk conditions are poorly defined in the research and so the actual increase in risk from each condition is unclear. Having two or more health conditions places an individual at higher risk than having one health condition. Heart disease (including high blood pressure), chronic kidney disease, pregnancy, obesity, stroke, diabetes and COPD are associated with severe illness. Cancer and immune suppression did not appear significant in this review, but experience says that active cancer and some forms of immune suppression may add substantial risk.

Authorship and Committee Members

Name	Contribution
Rachael Erdmann	Writing – evidence extraction, original draft preparation
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Topic: Risk Factors for Severe COVID-19 Outcomes [Updated November 19, 2021]

What risk factors (including but not limited to age, medical conditions, or lifestyle factors) are associated with the development of severe outcomes from COVID-19?

Context

- This review is an update of a SAG review conducted in August 2020 to identify risk factors for hospitalization, ICU admission, and mortality related to COVID-19. In this update, only meta-analyses were included in an attempt to capture more robust measures of association that may not be captured in primary studies.
- The purpose of this review is to provide information about who is at highest risk of severe outcomes, defined as hospitalization, ICU admission or death. Risk factors evaluated included age, comorbidity and immune compromise.
- Characterization of patients at risk of severe disease, along with trial results for individual therapies, can inform prioritization decisions, focus emerging or expensive therapies on patients most likely to benefit, and enhance cost-effectiveness and system sustainability.

Methodology and Terminology Note

A classification scheme was devised in the first version of this review to characterize and reconcile the measures of association identified in the evidence with the potential clinical importance of a statistically significant association. Two terms are used to describe the compiled evidence: “strength” and “consistency”.

Strength of association is guided by the observations of Chen, Cohen, & Chen (2010), but has been modified to account for clinical importance when the risk or odds of severe COVID would otherwise be considered to have no association:

- Low strength association: not significant (n.s.), OR <1.67 or HR/RR <1.5
- Moderate strength association: OR 1.68-3.47; HR/RR 1.5-2.5
- High strength association: OR>3.47 or HR/RR >2.5

Consistency is determined as follows:

- High consistency: all relevant studies show an association of similar strength
- Moderate consistency: (≥ 80% relevant studies show an association, but the strength of the association is variable
- Low consistency: more than 50% of findings show no effect

Given short timelines for this update, the search was restricted to English-language systematic reviews & meta-analyses published in 2021. Following de-duplication and screening, 69 articles were determined to be suitable for inclusion in the narrative synthesis (see Methods, Appendix C). Methods for each included article were screened for adequacy but not formally appraised; nor were the source studies reviewed in detail, which may reduce the overall certainty of the findings presented here. In most cases, the included studies have selected a specific patient population of interest and

considered different interacting factors in their analysis without adjusting for the interaction (i.e. univariate analysis). A scoring system has been developed for the United Kingdom that can calculate specific risk of severe outcomes, with or without vaccination (QCovid Risk Assessment)

Key Messages from the Evidence Summary

- Contributing studies were performed mainly during a pre-vaccination time frame reflecting primarily infection with the original COVID-19 wild type strain; therefore may not accurately identify risk factors for recent variants of concern or for post-vaccination breakthrough infection.
- While vaccination status was not part of the evidence in this review, not being vaccinated is known to be a very strong risk factor for severe disease; among the factors in this review, Age is the most important risk stratification marker. Although not the focus of this evidence review, vaccination is an important risk factor for severe disease. Strong evidence for the protective effect of vaccines has been published and summarized elsewhere by the COVID-END consortium. Table 1 below summarizes conditions that have moderate or high consistency across meta-analyses for association with COVID-19 hospitalization, ICU admission, or death. For most risk factors, associations are inconsistent because of study size, methodology, and population heterogeneity. Risk factors may be additive or synergistic, and the presence of more than one increases the risk of severe COVID-19. Because strength of association is based on relative risk (eg. OR, HR, RR) compared to individuals without the condition in question, this table does not reflect the absolute risks associated with a particular condition, which may be minimal but still have a consistent, high strength association.

Table 1. Association between risk factors and severe COVID-19 outcomes.

Risk Factor	Outcome	Strength of Association*	Consistency of meta-analysis results**	Meta-analyses included (N)
Age	ICU admission	High	Not applicable (n/a)	1 (5 studies)
	Mortality	Moderate-high	High	4
Cardiovascular disease	Hospitalization	High	n/a	1 (6 studies)
	ICU admission	Moderate-high	Moderate	4
	Mortality	Moderate-high	Moderate	10
Kidney disease	Hospitalization	Moderate-high	Moderate	2
	ICU admission	Low-moderate	Low	3
	Mortality	Moderate-high	Moderate	10
Cerebrovascular disease	ICU admission	Moderate-high	Moderate	4
	Mortality	Moderate	Moderate	5
Pregnancy	ICU admission	Moderate-high	Moderate	2
	Mortality	Moderate	Low	2
Hypertension	Hospitalization	Moderate	n/a	1 (9 studies)
	ICU admission	Moderate	Low	3
	Mortality	Moderate	Moderate	9

Risk Factor	Outcome	Strength of Association*	Consistency of meta-analysis results**	Meta-analyses included (N)
Diabetes	Hospitalization	Moderate	n/a	1 (8 studies)
	ICU admission	Low-moderate	Moderate	3
	Mortality	Moderate	Moderate	12
COPD	Hospitalization	Low-moderate	Low	3
	ICU admission	Low-moderate	Low	5
	Mortality	Moderate	Moderate	10
Obesity (BMI ≥ 30)	Hospitalization	Low-moderate	Moderate	4
	ICU admission	Low-moderate	Moderate	5
	Mortality	Low-moderate	Low	12
Cancer (undefined)	Hospitalization	Not significant	n/a	1 (4 studies)
	ICU admission	Low-moderate	Moderate	3
	Mortality	Low-moderate	Low	6

*Low strength associations (not significant (n.s.), OR <1.67 or HR <1.5); moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5); and high strength associations (OR>3.47 or HR/RR >2.5).
**High consistency (all relevant studies show an association of similar strength); moderate consistency (≥ 80% relevant studies show an association, but the strength of the association is variable); low consistency (more than 50% of findings show no effect)

- Age has a moderate to high-strength association with intensive care unit (ICU) admission and mortality. Age cut-offs were poorly defined in the literature and not standardized; however, age is not a categorical risk factor. Unpublished data from Alberta suggest that risk increases exponentially above 40 years of age and is strongly related to vaccination status.
- In reviewed papers, age interacts with all of the comorbidities identified to increase the risk of mortality from COVID-19. In general, increasing age amplifies the risk of COVID-19 severe outcomes when combined with any other comorbidity.
- Male sex has a weak, inconsistent association with severe COVID-19.
- Smoking has a weak, inconsistent association with severe COVID-19.
- Obesity, defined as body mass index (BMI) above 30, has a consistent, weak to moderate strength association with hospitalization and ICU admission, but an inconsistent association with mortality. The odds of mortality due to weight incrementally increase by 6% with every 1 kg/m^2 increase in BMI above 18 (OR 1.06 95% CI: 1.02–1.10).
- Diabetes was poorly defined in the literature and was rarely characterized (Type I and Type 2; duration and associated complications, etc). Regardless, there was a relatively consistent low-moderate strength association with hospitalization, ICU admission, and mortality.
- Hypertension has a relatively consistent moderate to strong association with hospitalization, ICU admission, and mortality. There appears to be a notable inverse interaction effect with age, where the effect is stronger in younger age groups, but this may be a confounded association.

- Cardiovascular disease (CVD) was poorly defined in the literature, but included coronary artery disease (CAD) / coronary heart disease (CHD), heart failure (HF), acute cardiac injury, and dysrhythmia. Regardless of subtype, CVD had a consistent moderate to strong association with severe outcomes from COVID-19.
- Pulmonary disease was inconsistently defined, however, most studies addressed chronic obstructive pulmonary disease (COPD) and asthma. Asthma is consistently **not associated** with severe COVID-19. COPD has an inconsistent weak to moderate strength association with hospitalization and ICU admission and a consistent moderate strength association with mortality.
- Kidney disease was commonly analyzed but not well defined. It had a consistent moderate to high strength association with hospitalization and mortality, but an inconsistent association with ICU admission. The latter may be a spurious finding influenced by care goals or health system and patient-specific factors rather than a result of a true biological interaction.
- Liver disease was not frequently considered as a comorbidity of interest and was often undefined. There is a heterogeneous spectrum of liver diseases which may confer differing levels of risk but, overall, liver disease does not appear to be a risk factor for severe COVID-19. The association with hospitalization, ICU admission, and mortality are inconsistent and mostly statistically insignificant.
- Cancer was generally undefined in the contributing studies. Across the included studies, the associations between cancer and hospitalization, ICU admission, and mortality are inconsistent, but weak-moderate at best. Unfortunately, cancer type (eg. non-melanoma skin cancer vs. lymphoma) and patient status (e.g. active treatment vs. cancer survivor) were not distinguished, and are likely to confer differential COVID risk.
- Meta-analyses on pregnancy and COVID-19 focused on fetal & newborn outcomes and the effect of infection on the pregnancy, rather than the effect of COVID-19 on the mother. In the two studies that addressed maternal outcomes of COVID-19, pregnancy had a moderate to high strength association with ICU admission, but an inconsistent association with mortality. This suggests that pregnancy is a risk factor for severe disease, but that pregnant patients have a high chance of survival due to their age and otherwise healthy status upon admission to ICU.
- Cerebrovascular disease was undefined and its associations with outcomes were inconsistent. On balance the evidence suggests that individuals with cerebrovascular disease have moderately increased odds of ICU admission and mortality from COVID-19.
- Receiving an organ transplant was inconsistently associated with mortality from COVID-19 and in most cases, not a significant risk factor. Likewise, immunodeficiency or immunosuppression was not significantly associated with mortality or ICU admission in subgroup analyses. In both cases, the grouping of heterogenous and undefined transplant and immune deficiency types may conceal important subgroup risks.

Committee Discussion

The committee supported the recommendations as presented, with no dissenters. The discussion centred around the best way to communicate a clear model for ranking the risk status of COVID-19 patients, when the limitations of the evidence and methods selected for the review do not lend themselves to a clear answer to the research question.

Most notably absent from the meta-analytic evidence were the bodies of research pertaining to SARS-CoV-2 variant strains, post-vaccination risk factors for breakthrough infection, and socioeconomic/sociodemographic factors. Source studies for the included meta-analyses were performed mainly throughout 2020 (i.e. pre-vaccination) and generally reflect infection with the original COVID-19 wild type strain. Accordingly, the analysis contained here may not accurately identify risk factors for recent variants of concern or for post-vaccination breakthrough infection. Primary studies from late 2021 suggest that specific risk factors for post-vaccination severe COVID-19, beyond the factors identified here, include: Down's syndrome, kidney transplantation, sickle cell disease, congregate living, chemotherapy, HIV/AIDS, liver cirrhosis, neurological conditions, recent bone marrow or solid organ transplant ever, dementia, and Parkinson's disease (Hippisley-Cox et al., 2021).

The univariate methodology of the included meta-analyses also poses a challenge in interpreting the evidence presented here. There have been some high-quality, large-scale cohort studies published in 2021 that offer multivariate statistical methods to be able to quantify the risk from each factor in isolation. It could be argued, however, that the presence of confounding in the results and the interactions between risk factors is more reflective of real world experience – an individual with COVID-19 is not a collection of isolated risk factors. Their true risk is a result of the interactions between all of their personal characteristics and clinical history.

Recommendations

1. The summary of risk factors from the first version of this review is still broadly valid. The current update adds clarity with respect to asthma, cardiovascular disease, hypertension, and kidney disease. The evidence for age as a risk factor was strengthened.
2. For the purposes of risk-stratification, a three-level approach is appropriate (see Figure 1 in practical considerations):
    a. Vaccination status is a key outcome determinant. Unvaccinated patients should be considered high risk, particularly those over the age of 50. Vaccine effectiveness may vary with age and health status (particularly in immunosuppressed individuals), and wanes over time. These factors should be considered when assessing individual patient susceptibility.
    b. Age is a powerful predictor of severe outcomes. Risk increases with age and appears to rise exponentially over age 40, particularly in unvaccinated patients.
    c. Patient comorbidity comprises the third level of risk stratification. Because of poor comorbidity definitions in source studies and broad grouping of

heterogeneous conditions, the actual level of risk associated with each identified comorbidity remains uncertain. Comorbidities may have additive risk, and combinations of two or more probably portend higher risk. Table 1 provides a crude summary of comorbidity-related risk. Cardiovascular disease (including hypertension), chronic kidney disease, pregnancy, obesity, cerebrovascular disease, diabetes and COPD are associated with hospitalization, ICU admission and death. Although cancer and immune suppression did not appear significant in this review, the committee felt, based on other high-quality evidence (Kartsonaki, preprint), that active cancers (particularly hematopoietic) and some forms of immune suppression pose substantial risk.

3. This review should be considered for update in 6-12 months, when the body of evidence has evolved to include evidence from variant SARS-CoV-2 strains and post-vaccination breakthrough infections.

Practical Considerations

- Age and BMI have a dose-response effect with respect to the risk of severe COVID-19; that is, risk of severe outcomes increases per unit increase (per 5-10 years of age; per 5 BMI).
- The conditions listed here are not an exhaustive list of risk factors. The true risk of comorbidities discussed here may be overestimated or underestimated based on the review strategy and statistical methods used in each meta-analyses. In addition, severe comorbidities (e.g. CKD, CVD) are almost certainly associated with greater risk than mild disease, and clinicians should consider overall clinical stability when assessing an individual's risk of severe outcomes from COVID-19.
- Immunosuppression or immunodeficiency did not appear to be a risk factor for severe COVID-19 outcomes; however, this is not congruent with conventional wisdom about infectious disease. This could be due to confounding risk behaviours, additional comorbidities, insufficient data to conduct risk stratification, or inadequate identification of important immune suppressed subgroups. Further, immunocompromised persons may have a suboptimal response to vaccination. A previous SAG review examined the risk of severe COVID-19 outcomes associated with immunosuppression and reported the following population groups at increased risk of severe outcomes and may have a poor response to vaccination:
    - Patients with active cancer should be considered to be at increased risk of COVID-19 and severe outcomes based on the limited data available. Hematologic and lung cancers should be considered highest risk of severe COVID-19 outcomes among patients with active cancer. In additional to previously identified risk factors, relapsing or progressive cancers, functional disability, lymphopenia <0.5/L, and severe hypogammaglobulinemia <4g/L should be considered to increase the risk of severe COVID-19

- Young patients with autoimmune disease in remission without additional medical co-morbidities are likely not at increased risk of severe outcomes of COVID-19.
- The following risk factors should be considered to be associated with an increased risk of severe COVID-19 outcomes in patients with autoimmune disease: older age (>65), comorbidities (obesity, chronic lung disease, cardiovascular disease, hypertension), active or progressive autoimmune disease, systemic rheumatologic disease (e.g. SLE, CTD)
- Chronic kidney disease should be considered to be associated with increased risk of COVID-19 and severe outcomes, especially in patients who are on renal replacement therapy.
- Corticosteroid use: more data on risk of COVID-19 in corticosteroid use stratified by dose is needed. In the interim, chronic (> 14 days) corticosteroid use of prednisone equivalent >10mg/day are considered to be associated with an increased risk of recognized COVID-19 and severe outcomes. The available evidence suggests that other immunosuppressive therapies are not associated with increased risk of COVID-19 or severe outcomes, although this does not include the risk of developing other non-COVID-19 related infections. There is limited data on individual therapies, and more data on the risks of COVID-19 in these populations as COVID-19 is expected restrictions are lifted.

- Figure 1 below shows a graphical description for stratifying the risk of severe outcomes for any given patient. This is not a validated predictive model and should not be used as such.

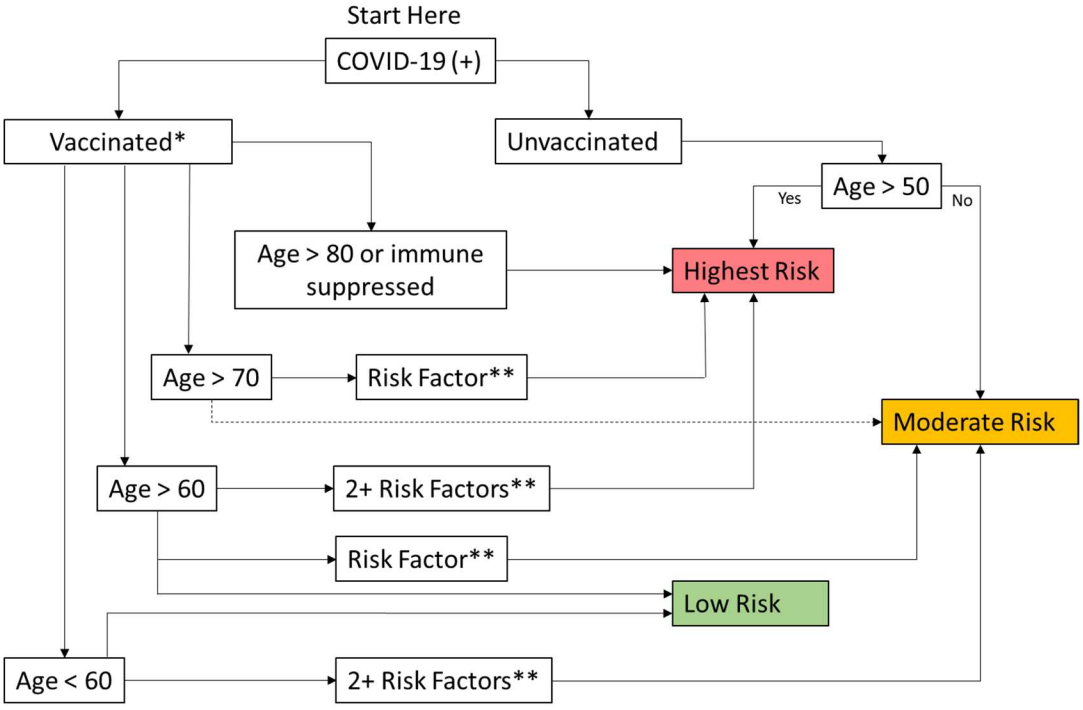

Figure 1. Graphical description for COVID-19 risk stratification.

*Vaccine effectiveness may differ based on age or other health factors (e.g. immunosuppression) and may wane after approx. 6 months

**Risk factors include cardiovascular disease (incl. hypertension), cerebrovascular disease†, CKD†, COPD, diabetes†, obesity, active cancer†, immunosuppression†, and pregnancy.

†These risk factors are poorly defined in source studies.

Research Gaps

- No meta-analytic evidence was identified regarding the risk factors for COVID-19 caused by variant strains of SARS-CoV-2. As variant strains are now the dominant strain circulating in Alberta, this is a critical gap in the literature.
- No meta-analytic evidence is yet available regarding the characteristics of individuals who experience severe COVID-19 after a full vaccine series.
- No meta-analytic evidence was identified in the database search regarding the role of socioeconomic factors or race/ethnicity in severe COVID-19. It has been shown that these elements interact with other risk factors (such as age) to increase risk of severe disease (Jin et al., 2020)
- No evidence was identified describing risk factors for severe COVID-19 in pediatric populations; however, local experience suggests that children have very favourable COVID-19 prognosis.
- Most articles included here conducted univariate analyses, which does not account for the confounding effects of co-occurring risk factors (eg. cardiovascular disease and hypertension; age and frailty; diabetes and obesity)
- Poor definitions of comorbidities was ubiquitous in the evidence, and severely limits the interpretation of the odds or risk ratios presented here. This impacts all of the risk factors described here, but is particularly important in categories like cancer, chronic kidney disease, and immunosuppression, where there is a broad spectrum of etiology, severity, and relevance to COVID-19 susceptibility.

Strength of Evidence

In general, the meta-analyses included in this review appear to be of reasonable quality. All included their search strategies, a PRISMA diagram, a funnel plot analyzing publication bias, and considered heterogeneity in their statistical analysis. Findings were inconsistent with respect to confounding and interaction effects; some authors performed meta-regression to identify confounders, others used pre-adjusted data, and some did not address interaction effects at all.

We did not evaluate the quality of the source studies underpinning the meta-analyses; however, primary studies on COVID-19 epidemiology often are of moderate quality at best. The commentary on quality in the previous SAG review on this topic likely still stands: over-representation of the COVID-19 experience from the eastern United States, Italy, and China may have overlapping datasets that could bias the measures of association away from the null.

All of the evidence included in the meta-analyses was collected throughout 2020 and the early part of 2021, making it representative for wild-type SARS-CoV-2. However, it is still too early for systematic reviews of Alpha and Delta variants or of patients with severe post-vaccination breakthrough infections to be available. This limits the applicability of this review; however, while the absolute risk associated with SARS-CoV-2 variants may differ, the risk factors likely have similar relative effects on patient outcome as they do with wild type SARS-CoV-2.

Limitations of this review

This review is not intended to be a systematic umbrella review of reviews. While the search strategy was thorough, we only included articles published in English in 2021 to manage the scope of this project. This time frame is useful for capturing evidence related to wild-type COVID-19, but is still too early to capture most of the evolving evidence relating to variant SARS-CoV-2 strains. In addition, there is a high likelihood of overlapping studies in our review of meta-analyses that may falsely suggest consistency or overestimate the effect of a given risk factor.

As with the previous iteration of this review, comorbid conditions of interest were poorly defined in the source literature. This is challenging when a single disease concept (such as kidney disease or cerebrovascular disease) is used to characterize an association arising from patients with a wide spectrum of illness severity.

Summary of Evidence

The research librarian searched Ovid Medline, Embase, and MedRxiv for systematic reviews and meta-analyses published in English in 2021. Following deduplication and initial screening by the librarian for obvious irrelevancy, 303 articles were forwarded for consideration based on the inclusion and exclusion criteria outlined in the methods section in Appendix C. After abstract screening and full text review, sixty-nine articles were included in the final synthesis.

What risk factors (including but not limited to age, medical conditions, or lifestyle factors) are associated with the development of severe outcomes from COVID-19?

Evidence from the primary literature

Due to the volume of epidemiological evidence available on COVID-19 and the availability of secondary analyses, primary studies were not eligible for inclusion in this report update.

Evidence from the secondary literature

Only secondary literature was considered for inclusion in this review. For more information on each study, the full evidence extraction table is included in Appendix B.

As discussed in the terminology note, the evidence presented here is classified according to a novel scheme that was devised for the first version of this review. The interpretation of the strength of association is guided by the observations of Chen, Cohen & Chen (2010), who show the relationship between Cohen's d and odds ratio (OR), hazard ratio (HR), or risk ratio (RR). By their rules, a moderate to strong association occurs when most studies show OR>3.47 or HR/RR >2.5; a weak association occurs when most studies show OR 1.68-3.47; HR/RR 1.5-2.5; and no association when OR < 1.67 and HR/RR <1.5 (Chen, Cohen & Chen, 2010). However, this model does not account for the potential clinical significance of increased odds, hazard, or risk that might be present in the "no association" category.

To assist with clarity and reconcile the potential clinical importance of the association with statistical significance, the tables presented below have been colour-coded. Low

strength associations (not significant (n.s.), OR <1.67 or HR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey, and associations that appear to be protective are not shaded in this analysis.

Interactions between risk factors

The effect of interactions between risk factors for severe COVID-19 is complicated. In some cases, various comorbid conditions may interact to result in higher risk of severe outcomes, while in other cases the interaction lowers the risk. The best example of this is age. On its own, age is a key risk factor for severe outcomes from COVID-19 (Pijls et al., 2021; Dessie & Zewotir, 2021; Du, Wang, Li et al., 2021; Xiang et al., 2021). When age is considered in the context of an individual with diabetes or other cardiovascular disease, the risk appears to increase in younger individuals as those who are under 50 with heart disease may be more unhealthy, generally, than those who have developed heart disease over age 60 (Bae et al., 2021).

In most cases, the articles included here have selected a patient population of interest and studied various risk factors without adjusting for interactions between these factors (i.e. univariate analysis of each risk factor).

Age

Compared to the findings in the first iteration of this review, age as a risk factor for severe COVID-19 was more commonly reported as a factor that interacted with other comorbidities than as a risk factor on its own. No meta-analyses were identified that described the association between age and hospitalization. One study reported the association between age and ICU admission (table 2), and four studies reported the association between age and COVID-19 mortality (table 3).

As a risk factor for severe COVID-19, age has a moderate to high-strength association with ICU admission and mortality. Age cut-offs were poorly defined in the literature and not standardized but fell between age 60 and 70; however, this incorrectly suggests that age is a binary risk factor. Although out of scope of the methods for the review, preprint data from the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort and unpublished evidence from Alberta suggests that age is a continuous variable where risk of severe outcomes increases as age increases (Kartsonaki, preprint; Saini et al., unpublished). None of the included meta-analyses examined risk increase per unit of age.

Table 2. Association between age and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Pijls et al.	Any	Age ≥ 70 (n= 688; 5 studies)	ICU Admission (Age <70)	RR 2.70 (1.59-4.60)	I^2= 69 Random effects model

Table 3. Association between age and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Dessie & Zewotir, 2021	Any	Undefined "older" age (n= 21 studies)	Mortality (younger age)	pOR 2.61 (1.75–3.47)	I^2= 99.9 Mixed effect model
Du, Wang, Li et al.	Any	Age ≥ 60 years (n=1168; 3 studies))	Mortality (age < 60)	OR 6.00 (3.48–10.34)	I2 = 31% Fixed effects model
Pijls et al.	Any	Age ≥ 70 (n= 9222; 5 studies)	Mortality (Age <70)	RR 3.61 (2.70-4.84)	I^2= 60 Random effects model
Xiang et al.	Any	Age ≥ 60 years (n= 7 studies)	Mortality (age < 60 years)	OR 4.94 (2.89-8.44)	I^2=86 Random effects model

Sex

In meta-analysis with large study populations, male sex is weakly associated with severe outcomes of COVID-19. One study described the association between sex and hospitalization (table 4), and six studies described the association between sex and mortality (table 5). One included study (Xiang et al., 2021) analysed sex as a risk factor, however, uses male as the reference (instead of female, as the other included studies). Xiang (2021) found that females had 44% reduced odds of mortality from COVID-19 (OR 0.66 (0.59-0.73)) when data from 20 studies was combined (I^2= 29.3). Although not the same measure, this also suggests a low increase in risk for males when the inverse odds are calculated.

Taken together, these studies show that males experience higher risk; however, this association is inconsistent and weak at best.

Table 4. Association between sex and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Pijls et al.	Any	Male sex (n=1493; 11 studies)	ICU admission (female)	RR 1.38 (1.09 - 1.74)	I^2= 32 Random effects model

Table 5. Association between sex and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Male (5 studies)	Mortality (female)	RR 0.98 (0.67; 1.43)	I^2= 89.3
Bachul et al.	Kidney transplant recipients	Male (n= 22 studies)	Mortality (female)	OR 0.71 (0.50–1.01)	I^2 = 0% Random effects model
Dessie & Zewotir	Any	Male sex (n= 15 studies)	Mortality (female)	pOR 1.45 (1.41–1.51)	I^2= 66.7 Mixed effect model
Du, Wang, Li et al.	Any	Male sex (n=302; 7 studies)	Mortality (female)	OR 1.54 (1.13-2.10)	I^2= 10% Fixed effects model
Pijls et al.	Any	Male sex (n= 12792; 14 studies)	Mortality (female)	RR 1.50 (1.18-1.91)	I^2= 62 Random effects model
Taylor et al.	Any	Male sex (n= 55 studies)	Mortality (female)	OR 1.13 (0.98-1.31)	I^2=81.7 Random effects model

Smoking

Five studies were identified that described the association between smoking and severe outcomes from COVID-19 (tables 6-8). In most cases, it was unclear how the analysis defined smoking (such as current smoking, former smoking, or any history of smoking). On its own, smoking appears to be inconsistently associated with severe COVID-19, with a weak association at best. No study considered how smoking may result in additional, stronger risk factors for COVID-19 (such as lung disease, cancer, and cardiovascular complications).

Table 6. Association between smoking and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	Smoking (8 studies)	Hospitalization (no smoking)	OR 1.04 (0.7-1.54)	I^2= 60.5 Random effects model

Table 7. Association between smoking and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	Smoking (9 studies)	ICU admission (no smoking)	OR 1.00 (0.77-1.29)	I^2= 17.1 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Zhang, Ma, Han et al.	Smoking history	Any smoking (n= 14 studies)	ICU admission (never smoked)	OR 1.73 (1.36-2.19)	I^2=55.6 Random effects model

Table 8. Association between smoking and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Smoking (1 study)	Mortality (no smoking)	RR 0.74 (0.32; 1.71)	I^2= none
Dessie & Zewotir	Any	Smoking 5 studies	Mortality (no smoking)	pOR 1.42 (1.01–1.83)	I^2= 55.8 Mixed effect model
Katzenschlager et al.	Any	Smoking (22 studies)	Mortality (no smoking)	OR 1.36 (1.10-1.67)	I^2= 10.5 Random effects model
Poly et al.	Obesity	Smoking (6 studies)	Mortality (no smoking)	RR 1.13 (0.91-1.40)	I^2= 46.6 Random effects model
Zhang, Ma, Han et al.	Smoking history	Any smoking (n= 44 studies)	Mortality (never smoked)	OR 1.58 (1.38-1.81)	I^2=79.5 Random effects model

Obesity

Obesity was a commonly considered comorbidity in studies of COVID-19 severe outcomes, however, was not always defined in the literature. In the studies that defined their body mass index cutoffs, obesity can be considered to be a body mass index (BMI) of at least 30, while overweight can be classified as a BMI between 25 and 30. Non-obese is classified as BMI ≤ 25 (Du, Lv, Zha et al, 2021; Helvaci et al., 2021; Hoong et al., 2021; Seidu et al., 2021; Yang, Tian, Chen et al., 2021; Zhang, Lewis, Moley et al, 2021). In the articles included in the tables below, “obesity” was undefined unless specifically

Obesity on its own has a weak to moderate strength association with hospitalization and ICU admission (tables 9 & 10), but an inconsistent association with mortality (table 11). This discrepancy may suggest that obesity is only weak risk factor on its own, but has interaction effects with other comorbidities (Du, Lv, Zha et al., 2021; Poly et al., 2021) or may indicate a high likelihood of having other risk factors for severe COVID-19 (Poly et al., 2021).

Notably, obesity has an in incremental increase in association with risk per unit of BMI. Du, Lv, Zha et al. (2021) calculated that odds of mortality increase by 6% with every 1 kg/m^2 increase in BMI above 18 (OR 1.06 95% CI: 1.02–1.10). The association of BMI and mortality was also examined by Deng et al (2021), however, at 5 kg/m^2 increase in

BMI did not reach statistical significance. This may be an artifact of methodological differences between the two analyses, as it is unlikely that a 1 unit increase in BMI is significant but a 5 unit increase is not.

Table 9. Association between obesity and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Cai, Yang & Zhang	Obesity	Hospitalization outcome (n= 396603; 5 studies)	Hospitalization (non-obese)	OR 1.72, (1.55-1.92)	I^2= 47.4% Fixed effects model
Helvaci et al.	Obesity	Hospitalization outcome (n= 6952;5 studies)	Hospitalization (BMI <30)	OR 1.3 (1.00-1.69) p=0.05	I^2= 52% Random effects model
Yang, Tian, Chen et al.	Obesity	Obesity (n= 25,403)	Hospitalization (no obesity)	OR = 1.54, (1.33–1.78)	I^2=60.9 Random effects model
		BMI 25-30	Hospitalization (BMI <25)	OR = 1.30 (1.09–1.57)	I^2=0 Random effects model
		BMI 30-40	Hospitalization (BMI <25)	OR = 2.09, (1.34–3.26)	I^2=95 Random effects model
		BMI ≥ 40	Hospitalization (BMI <25)	OR = 2.76, (1.76–4.32)	I^2=25.8 Random effects model
Zhang, Lewis & Moley et al.	Obesity	Hospitalization outcome (n= 6252; 4 studies)	Hospitalization (non-obese)	OR 1.68 (1.28-2.188)	I^2 not described Random effects model

Table 10. Association between obesity and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Cai, Yang & Zhang	Obesity	Mechanical ventilation outcome (n=2088)	MV (non-obese)	OR 1.66, (1.42–1.94)	I^2= 41.3% Fixed effects model
Geng et al.	Any	Obesity (undefined) (n= 242584)	ICU admission (no obesity)	OR 1.86 (1.49-2.31)	I^2=89.4 Random effects model
Helvaci et al.	Obesity	ICU Admission outcome	ICU admission (BMI <30)	OR 1.51 (1.16-1.97)	I^2= 72%

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		(n= 7038)			Random effects model
Yang, Tian, Chen et al.	Obesity	Obesity (n= 4086)	ICU admission (no obesity)	OR 1.48 (1.24-1.77)	I^2=67.5 Random effects model
		BMI 25-30	ICU admission (BMI <25)	OR = 1.90 (0.89–4.07)	I^2=0 Random effects model
		BMI 30-40	ICU admission (BMI <25)	OR = 1.44, (0.67–3.09)	I^2=0 Random effects model
		BMI ≥ 40	ICU admission (BMI <25)	OR = 2.19, (0.51–9.35)	I^2=63.8 Random effects model
Zhang, Lewis & Moley et al.	Obesity	ICU outcome (n= 8 studies)	ICU admission (Non-obese)	OR 1.35 (1.14-1.59)	I^2= not described Random effects model

Table 11. Association between obesity and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Obesity (no definition)	Mortality (no obesity)	RR 1.28 (0.78; 2.10)	I^2= 60.8
Cai, Yang & Zhang	Obesity	Mortality outcome (n= 29305)	Mortality (non-obese)	OR 1.61, (1.29–2.01)	I^2= 83.1% Random effects model
Deng et al.	Obesity	All studies (n= 5175)	Mortality (non-obese)	OR 1.05 (0.65–1.71)	I^2= 66.6% Random effects model
Dessie & Zewotir	Obesity	Obesity 9 studies	Mortality (non-obese)	pOR 1.34 (1.17–1.52)	I^2= 82.6 Mixed effect model
Du,Lv, Zha et al.	Obesity	BMI ≥ 30 (n= 14124)	Mortality (non-obese)	OR 2.68 (1.65–4.37)	I^2= 79.3 Random effects model
		BMI ≥ 35	Mortality (BMI 30-35)	OR 3.54 (1.48–8.48)	I^2= 72
Geng et al.	Any	Obesity (undefined)	Mortality (no obesity) (n= 155450)	OR 1.19, (0.94–1.51)	I^2= 93.0 Random effects model
		Morbid obesity (BMI ≥40)	Mortality (obesity) (n= 5531)	OR 0.98, (0.80–1.20)	I^2=0.0 Fixed effects model
Helvaci et al.	Obesity	Mortality outcome (n=9211)	Mortality (BMI <30)	OR 1.28 (0.76-2.16)	I^2= 80% Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Hoong et al.	Obesity	Mortality outcome (n=17322)	Mortality (BMI <30)	pOR 1.51 (1.13–2.21)	I^2= 46.2 Fixed effects model
Poly et al.	Obesity	Mortality outcome (16 studies)	Mortality (non-obese)	RR 1.42 (1.24–1.63)	I^2= 67.9 Random effects model
		Obesity * Age ≥ 65 (6 studies)	Mortality (Age < 65)	RR 2.54 (1.62-3.97)	I^2= 89.3 Random effects model
		Obesity * Male gender (6 studies)	Mortality (female)	RR 1.38 (1.25-1.51)	I^2= 9.6 Random effects model
		Obesity * diabetes (11 studies)	Mortality (non-diabetic)	RR 1.19 (1.07-1.32)	I^2= 54.2 Random effects model
		Obesity * hypertension (9 studies)	Mortality (no HTN)	RR 1.07 (0.92-1.25)	I^2= 60.6 Random effects model
		Obesity * CKD (7 studies)	Mortality (no CKD)	RR 1.57 (1.29-1.91)	I^2= 69.2 Random effects model
		Obesity * COPD (5 studies)	Mortality (no COPD)	RR 1.34 (1.18-1.52)	I^2= 16.1 Random effects model
		Obesity * Stroke (2 studies)	Mortality (no stroke	RR 1.80 (0.89-3.64)	I^2= 0 Random effects model
		Obesity * Smoking (6 studies)	Mortality (no smoking)	RR 1.13 (0.91-1.40)	I^2= 46.6 Random effects model
Seidu et al.	Obesity	BMI ≥ 25 (n= 4 studies)	Mortality (BMI <25)	RR 3.52 (1.32-9.42)	I^2= 66% Random effects model
Yang, Tian, Chen et al.	Obesity	Obesity (n= 8259)	Mortality (no obesity)	OR 1.14 (1.04-1.26)	I^2=74.4 Random effects model
		BMI 25-30	Mortality (BMI < 25)	OR = 1.06, (0.79–1.42)	I^2=0 Random effects model
		BMI 30-35	Mortality (BMI < 25)	OR = 1.01, (0.74–1.39)	I^2=0 Random effects model
		BMI 35-40	Mortality (BMI < 25)	OR = 1.32, (0.88–1.96)	I^2=0 Random effects model
		BMI ≥ 40	Mortality (BMI < 25)	OR = 1.56, (1.07–2.26)	I^2=0 Random effects model
Zhang, Lewis, Moley et al.	Obesity	Mortality outcome (n= 9 studies)	Mortality (non-obese)	OR 0.96 (0.74-1.25) (not stable in sensitivity analysis)	I^2= not described Random effects model

Diabetes

Diabetes was commonly considered in the meta-analyses as a comorbidity of interest for severe COVID-19; however, most articles did not clearly define the type and severity of diabetes considered in the analysis (simply saying “diabetes”). One study examined the association between diabetes and hospitalization (table 12), three studies examined the association with ICU admission (table 13), and 12 studies examined mortality (table 14).

Diabetes has a relatively consistent low-moderate strength association with hospitalization, ICU admission, and mortality. The analyses by Schlesinger et al. (2021) and Bae et al. (2021) suggest that diabetes interacts with age to increase the risk of mortality in individuals infected with SARS-CoV-2.

Table 12. Association between diabetes and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	Diabetes (8 studies)	Hospitalization (no diabetes)	OR 3.01 (1.99-4.56)	I^2= 77.1 Random effects model

Table 13. Association between diabetes and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Diabetes (n= 259522)	ICU Admission (no diabetes)	OR 2.50 (2.18-2.87)	I^2= 79.6 Random effects model
Hoang & Anh	Any	Diabetes	ICU admission (no diabetes)	RR 2.44 (1.66 - 3.60)	I^2= 44.5 Fixed effects model
Katzenschlager et al.	Any	Diabetes (22 studies)	ICU admission (no diabetes)	OR 1.58 (1.29-1.93)	I^2= 30.9 Random effects model

Table 14. Association between diabetes and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Diabetes	Mortality (no diabetes)	RR 1.90 (1.53; 2.37)	I^2= 62.7

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Bae et al.	CVD risk factors	Diabetes * Age < 50 (n= 6026)	Mortality (no diabetes)	OR 5.31 (3.22; 8.26)	Random effects model
		Diabetes * Age 50-60 (n= 9965)	Mortality (no diabetes)	OR 2.22 (1.82; 2.72)	Random effects model
		Diabetes * Age ≥ 60 (n= 27513)	Mortality (no diabetes)	OR 1.76 (1.27; 2.44)	Random effects model
Dessie & Zewotir	Any	Diabetes 13 studies	Mortality (no diabetes)	pOR 1.52 (1.36–1.69)	I^2= 79.83 Mixed effect model
Du, Wang, Li et al.	Any	Diabetes (n=4873)	Mortality (no diabetes)	OR 2.60 (2.03–3.34)	I^2= 9% Fixed effects model
Geng et al.	Any	Diabetes (n=307588)	Mortality (no diabetes)	OR 1.99 (1.82–2.18)	I^2= 84.8 Random effects model
Kaminska et al.	Diabetes	Mortality outcome (n= 6031)	Mortality (no DM)	OR 2.39 (1.65-3.46)	I^2= 62% Random effects model
Kandil et al.	Diabetes mellitus	All studies (n= 75200)	Mortality (no DM)	pOR 1.87 (1.51–2.31)	I^2= 77.9%
Katzenschlager et al.	Any	Diabetes (54 studies)	Mortality (no diabetes)	OR 2.14 (1.82-2.52)	I^2= 56.3 Random effects model
Palaidodimos et al.	Diabetes mellitus	n/a (all studies)	Mortality (no DM)	OR 1.65 (1.35-1.96)	I^2= 77.4 Random effects model
Schlesinger et al.	Diabetes	Diabetes * Male (n= 10 studies)	Mortality (female)	Summary RR 1.28 (1.02-1.61)	I^2= 28 Random effects model
		Diabetes * Age ≥ 65 (n=6 studies)	Mortality (Age < 65)	SRR 3.49 (1.82-6.69)	I^2= 74 Random effects model
		Diabetes * Age per 5 years (n= 5 studies)	Mortality	SRR 1.43 (1.12-1.83)	I^2= 84 Random effects model
		Diabetes * current smoking (n= 3 studies)	Mortality (non-smoking)	SRR 0.91 (0.79-1.06)	I^2= 0 Random effects model
		Diabetes * overweight (n= 2 studies)	Mortality (normal weight)	SRR 0.72 (0.45-1.16)	I^2= 0 Random effects model
		Diabetes * Obesity (n= 4 studies)	Mortality (non-obese)	SRR 1.06 (0.76-1.49)	I^2= 46 Random effects model
		Diabetes * Hypertension (n= 8 studies)	Mortality (no HTN)	SRR 1.09 (0.77-1.53)	I^2= 41 Random effects model
		Diabetes * CVD (n= 8 studies)	Mortality (no CVD)	SRR 1.56 (1.09-2.24)	I^2= 70 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		Diabetes * Cerebrovascular disease (n= 2 studies)	Mortality (no CeVD)	SRR 2.11 (1.36-3.26)	I^2= 0 Random effects model
		Diabetes * CKD (n= 6 studies)	Mortality (no CKD)	SRR 1.93 (1.28-2.90)	I^2= 81 Random effects model
		Diabetes * COPD (n= 5 studies)	Mortality (no COPD)	SRR 1.40 (1.21-1.62)	I^2= 0 Random effects model
		Diabetes * Cancer (n= 3 studies)	Mortality (no cancer)	SRR 1.54 (0.94-2.51)	I^2= 0 Random effects model
		Diabetes * Any comorbidity (n= 2 studies)	Mortality (no comorbidity)	SRR 0.94 (0.45-1.98)	I^2= 42 Random effects model
Taylor et al.	Any	Diabetes (n= 47 studies)	Mortality (no diabetes)	OR 1.41 (1.22-1.63)	I^2=63.2 Random effects model
Xiang et al.	Any	Diabetes (n= 17 studies)	Mortality (no diabetes)	OR 1.63 (1.44-1.84)	I^2=29.1 Random effects model

Hypertension

Ten studies were identified that examined the association between hypertension and severe COVID-19 outcomes (tables 15-17). Hypertension had a relatively consistent moderate to strong association with hospitalization, ICU admission, and mortality. There appears to be a notable inverse interaction effect with age – Bae et al. (2021) found that younger individuals (under age 50) with hypertension were strongly associated with mortality. This could be a confounded effect, since if an individual is under 50 and has high blood pressure, they may have other interacting comorbidities.

Table 15. Association between hypertension and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	Hypertension (9 studies)	Hospitalization (no HTN)	OR 3.28 (2.21-4.87)	I^2= 80.6 Random effects model

Table 16. Association between hypertension and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47

or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Hypertension (n= 259220)	ICU Admission (no HTN)	OR 2.24 (1.90-2.63)	I^2 = 87.1 Random effects model
Hoang & Anh	Any	Hypertension	ICU admission (no HTN)	RR 2.64 (2.03 - 3.44)	I^2= 1.9 Fixed effects model
Katzenschlager et al.	Any	Hypertension (22 studies)	ICU admission (no HTN)	OR 1.62 (1.24-2.12)	I^2= 69.1 Random effects model

Table 17. Association between hypertension and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Hypertension	Mortality (no HTN)	RR 1.37 (1.24, 1.51)	I^2= 69.3
Bae et al.	Risk factors for CVD	Hypertension * Age < 50 (n= 6143)	Mortality (no HTN)	OR 6.13 (4.01; 9.39)	Random effects model
		Hypertension * Age 50-60 (n= 13111)	Mortality (no HTN)	OR 2.81 (1.97; 4.01)	Random effects model
		Hypertension * Age ≥ 60 (n= 10180)	Mortality (no HTN)	OR 2.10 (1.67; 2.64)	Random effects model
Dessie & Zewotir	Any	Hypertension 12 studies	Mortality (no HTN)	pOR 1.57 (1.27–1.87)	I^2 = 94.9 Mixed effect model
Du, Zhou, Zha et al.	Hypertension	Mortality outcome (adjusted) (n= 7212)	Mortality (no HTN)	OR 2.17; (1.67–2.82)	I^2= 67.3 Random effects model
		Age > 60 years	Mortality (HTN * Age ≤ 60)	OR: 3.12 (1.93 − 5.05)	I^2= 59.8 Random effects model
Du, Wang, Li et al.	Any	Hypertension (n=4158)	Mortality (no HTN)	OR 3.53 (2.49-5.01)	I^2=51% Random effects model
Geng et al.	Any	Hypertension (n= 254926)	Mortality (no HTN)	OR 2.31 (2.04–2.61)	I^2= 92.2 Random effects model
Katzenschlager et al.	Any	Hypertension (55 studies)	Mortality (no HTN)	OR 2.49 (2.11-2.94)	I^2= 69.4 Random effects model
Taylor et al.	Any	Hypertension	Mortality (no HTN)	OR 1.54 (1.29-1.85)	I^2=81.7

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		(n= 45 studies)			Random effects model
Xiang et al.	Any	Hypertension (n= 18 studies)	Mortality (no HTN)	OR 2.26 (1.73-2.95)	I^2=77.4 Random effects model

Cardiovascular disease

Cardiovascular disease (CVD) was a key comorbidity of interest in the included meta-analyses; however, was often not clearly defined thus strengthening the measure of association for some disease states and weakening the measure of association for others. Sub-categories identified in the evidence include coronary artery disease (CAD) / coronary heart disease (CHD), heart failure (HF), acute cardiac injury / cardiac injury, and arrythmia. Eleven studies were identified that examined the association between CVD and hospitalization (table 18), ICU admission (table 19), and mortality (table 20).

CVD, regardless of subtype, had a consistent moderate-strong association with severe outcomes from COVID-19. This is somewhat expected as the cell surface receptor for SARS-CoV-2, ACE2, is highly expressed within the cardiovascular system (Shang et al, 2020; Li, Li, Zhang et al., 2020). As with hypertension, there appears to be an inverse interaction effect with age that can be explained with confounding (Bae et al., 2021) – a younger individual with CVD is likely to have other comorbidities that increase their risk of severe outcomes from COVID-19.

Table 18. Association between CVD and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	CVD (6 studies)	Hospitalization (no CVD)	OR 3.85 (2.56-5.81)	I^2= 75.4 Random effects model

Table 19. Association between CVD and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Coronary heart disease (n= 22459)	ICU admission (no CHD)	OR 2.16 (1.56-2.99)	I^2=79.9 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		Heart failure (n= 28505)	ICU admission (no HF)	OR 1.80 (1.44-2.25)	I^2= 62.7 Random effects model
		Unspecified CVD (n= 220351)	ICU admission (no CVD)	OR 2.38 (1.92-2.96)	I^2= 54.8 Random effects model
Hoang & Anh	Any	Cardiovascular disease	ICU admission (no CVD)	RR 2.59 (1.61 - 4.16)	I^2= 0.0 Fixed effects model
Katzenschlager et al.	Any	CVD (17 studies)	ICU admission (no CVD)	OR 1.50 (0.99-2.28)	I^2= 78.0 Random effects model
Liang, Zhang, Li et al.	Coronary heart disease	ICU outcome (4 studies)	ICU admission (no CHD)	OR 2.25 [1.34, 3.79]	I^2= 0% Fixed effects model

Table 20. Association between CVD and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	CVD / Coronary artery disease	Mortality (no CVD)	RR 1.80 (0.85; 3.80)	I^2= 92.0
Bae et al.	CVD	CVD * Age < 50 (n= 5838)	Mortality (no CVD)	OR 7.80 (4.06; 15.00)	Random effects model
		CVD * Age 50-60 (n= 6124)	Mortality (no CVD)	OR 3.14 (1.12; 8.78)	Random effects model
		CVD * Age ≥ 60 (n= 24599)	Mortality (no CVD)	OR 2.46 (1.91; 3.17)	Random effects model
Dessie & Zewotir	Any	CVD 9 studies	Mortality (no CVD)	pOR 1.83 (1.50–2.17)	I^2= 41.27 Mixed effect model
		Cardiac Injury 3 studies	Mortality (no cardiac injury)	pOR 2.33 (0.88–3.79)	I^2= 6.0 Mixed effect model
Du, Wang, Li et al.	Any	CVD (n=4873)	Mortality (no CVD)	OR 4.91 (3.28,7.35)	I^2=44% Fixed effects model
Geng et al.	Any	Coronary artery disease (n= 46130)	Mortality (no CHD)	OR 2.46, (2.14–2.82)	I^2= 63.1 Random effects model
		Heart failure (n= 143780)	Mortality (no HF)	OR 2.74, (2.21–3.40)	I^2= 92.9 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		Unspecified CVD (n= 68579)	Mortality (no CVD)	OR 2.59, (2.24–3.00)	I^2= 79.3 Random effects model
Hessami et al.	CVD	Acute cardiac injury (n= 12 studies)	Mortality (no ACI)	pOR 13.29 (7.35, 24.03)	I^2= 74.3 Random effects model
		Heart failure (n= 8 studies)	Mortality (no HF)	pOR 6.72 (3.34, 13.52)	I^2= 86.8 Random effects model
		Arrhythmia (n= 3 studies)	Mortality (no arrhythmia)	pOR 2.75 (1.43, 5.25)	I^2= 0 Fixed effects model
		Hypertension (n= 31 studies)	Mortality (no HTN)	pOR 2.60 (2.11, 3.19)	I^2= 73.9 Random effects model
		Cardiovascular disease (n= 14 studies)	Mortality (no CVD)	pOR 2.61 (1.89, 3.62)	I^2= 55.5 Random effects model
		Coronary heart disease (n= 16 studies)	Mortality (no CHD)	pOR 3.78 (2.42, 5.90)	I^2= 76.2 Random effects model
Katzenschlager et al.	Any	CVD (36 studies)	Mortality (no CVD)	OR 3.93 (2.91-5.30)	I^2= 73.3 Random effects model
Liang, Zhang, Li et al.	Coronary heart disease	Mortality outcome (22 studies)	Mortality (no CHD)	OR 3.75 [2.91, 4.82]	I^2= 73.1% Random effects model
Taylor et al.	Any	Cardiovascular disease (n= 41 studies)	Mortality (no CVD)	OR 1.91 (1.52-2.38)	I^2=68.2 Random effects model
Xiang et al.	Any	Cardiovascular disease (n= 20 studies)	Mortality (no CVD)	OR 2.52 (2.21-2.89)	I^2=49.6 Random effects model

Pulmonary disease

Since COVID-19 primarily presents as a respiratory disease, there was a substantial body of evidence examining the association between pulmonary diseases and risk of severe outcomes. Pulmonary disease was inconsistently defined, however, most studies identified chronic obstructive pulmonary disease (COPD) and asthma as separate from unspecific lung disease.

Asthma is very clearly and consistently **not associated** with severe COVID-19. Of the nine unique studies reporting on hospitalization, ICU admission, and mortality, no analysis resulted in a significant association with severe outcomes. This is so apparent that outcomes from asthma have been compiled into a separate table (table 21) from all other pulmonary diseases so that it does not skew the estimation of risk due to COPD or other pulmonary disease.

Regarding other pulmonary diseases examined in the included meta-analyses (tables 22-24), there is an inconsistent weak to moderate strength association with hospitalization (table 22) and ICU admission (table 23), but a fairly consistent moderate strength association between pulmonary disease and mortality (table 24). No clear interaction effects were identified for pulmonary disease as a risk factor for severe COVID-19.

Table 21. Association between asthma and severe outcomes from COVID-19. . Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Associations that appear to be protective are not shaded. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Pardhan et al.	Asthma & COPD	Asthma (n= 1087689; 7 studies)	Hospitalization (no asthma)	OR 0.87 (0.73-1.04)	I^2= 85.4 Random effects model
Sitek et al.	Asthma	Hospitalization outcome (n= 4 studies)	Hospitalization (no asthma)	OR 1.26 (0.29-7.28)	I^2=86.5 Random effects model
Wu et al.	Asthma	Hospitalization outcome (n= 10 studies)	Hospitalization (no asthma)	OR 0.91 (0.76-1.10)	I^2=79.1 Random effects model
Geng et al.	Any	Asthma (n=227500)	ICU admission (no asthma)	OR 1.07 (0.94-1.22)	I^2=26.1 Fixed effects model
Liu, Cao, Du et al.	Asthma	Mechanical ventilation outcome (n= 3285; 4 studies)	Mechanical ventilation (no asthma)	RR 1.03 (0.72 -1.46)	I^2= 0.0 Random effects model
Pardhan et al.	Asthma & COPD	Asthma (n= 167849; 4 studies)	ICU admission (no asthma)	OR 0.75 (0.54-1.02)	I^2= 87.2 Random effects model
Sitek et al.	Asthma	ICU outcome (n= 6 studies)	ICU admission (no asthma)	OR 1.65 (0.65-4.17)	I^2=54.2 Random effects model
Wu et al.	Asthma	ICU outcome (n= 15 studies)	ICU outcome (no asthma)	OR 1.17 (0.81-1.68)	I^2=91.1 Random effects model
Geng et al.	Any	Asthma (n= 47470)	Mortality (no asthma)	OR 0.74 (0.68-0.80)	I^2= 0 Fixed effects model
Katzenschlager et al.	Any	Asthma (4 studies)	Mortality (no asthma)	OR 0.88 (0.58-1.35)	I^2= 0 Random effects model
Kaur et al.	Asthma	Mortality outcome (all) (n= 10028)	Mortality (no asthma)	OR = 0.96 (0.70–1.30)	I^2= 0 Random effects model
Liu, Cao, Du et al.	Asthma	Mortality outcome (n= 5000; 6 studies)	Mortality (no asthma)	RR 0.65; (0.43-0.98)	I^2= 0.0 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Pardhan et al.	Asthma & COPD	Asthma (n=876759; 7 studies)	Mortality (no asthma)	aOR 0.83 (0.12-0.96)	I^2= 61.5 Random effects model
Reyes et al.	Asthma & COPD	Asthma (n= 6 studies)	Mortality (no asthma)	OR 0.87 (0.66-1.14)	I^2= 10.1 Random effects model
Sitek et al.	Asthma	Mortality outcome (n=12 studies)	Mortality (no asthma)	OR 0.73 (0.38-1.40)	I^2=81.5 Random effects model
Wang, Chen, Chen et al.	Asthma	Mortality outcome (n= 4 studies)	Mortality (no asthma)	OR 0.96 (0.70-1.30)	I^2=0 Random effects model
Wu et al.	Asthma	Mortality outcome (adjusted) (n=21 studies)	Mortality (no asthma)	OR 0.95 (0.78-1.15)	I^2=63.5 Random effects model

Table 22. Association between pulmonary disease and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Gerayeli et al.	COPD	Hospitalization outcome (n= 350509)	Hospitalization (no COPD)	pOR 4.23 (3.65-4.90)	I^2= 27.3% Fixed effects model
Katzenschlager et al.	Any	Chronic lung disease (4 studies)	Hospitalization (no CLD)	OR 1.98 (1.04-3.74)	I^2= 61.0 Random effects model
Pardhan et al.	Asthma & COPD	COPD (n=588025; 6 studies)	Hospitalization (no COPD)	OR 1.39 (1.31-1.48)	I^2= 4.2 Random effects model

Table 23. Association between pulmonary disease and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	COPD (n=231641)	ICU Admission (no COPD)	OR 2.76 (1.99-3.82)	I^2=69.7 Random effects model
Gerayeli et al.	COPD	ICU outcome (n= 14549)	ICU admission (no COPD)	pOR 1.35 (1.02-1.78)	I^2= 41% Fixed effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Hoang & Anh	Any	COPD	ICU admission (no COPD)	RR 4.76 (2.44 - 9.27)	I^2= 0.0 Fixed effects model
Katzenschlager et al.	Any	COPD (12 studies)	ICU admission (no COPD)	OR 1.39 (0.90-2.16)	I^2= Random effects model
		Chronic lung disease (9 studies)	ICU admission (no CLD)	OR 1.06 (0.89 – 1.25)	I^2= 0.0 Random effects model
Pardhan et al.	Asthma & COPD	COPD (n= 197108; 9 studies)	ICU admission (no COPD)	OR 1.34 (1.14-1.57)	I^2= 66.6 Random effects model
Reyes et al.	Asthma & COPD	COPD (n= 6 studies)	ICU Admission (no COPD)	OR 1.39 (0.79-2.44)	I^2= 57.5 Random effects model

Table 24. Association between pulmonary disease and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	COPD	Mortality (no COPD)	RR 2.19 (1.54; 3.10)	I^2= 0.0
Dessie & Zewotir	Any	COPD 7 studies	Mortality (no COPD)	pOR 1.58 (1.08–2.07)	I^2 = 92.2 Mixed effect model
Du, Wang, Li et al.	Any	Chronic lung disease (n=4694)	Mortality (no lung disease)	OR 3.72 (2.00–6.94)	I^2= 61% Random effects model
Geng et al.	Any	COPD (n= 65928)	Mortality (no COPD)	OR 2.95 (2.48–3.50)	I^2=73 Random effects model
Gerayeli et al.	COPD	Mortality outcome (n=40457)	Mortality (no COPD)	pOR 2.47 (2.18-2.79)	I^2= 12.3% Fixed effects model
Katzenschlager et al.	Any	COPD (12 studies)	Mortality (no COPD)	OR 2.54 (1.87-3.44)	I^2= 39.4 Random effects model
		Chronic lung disease (18 studies)	Mortality (no CLD)	OR 3.12 (2.17-4.49)	I^2= 3.95 Random effects model
Pardhan et al.	Asthma & COPD	COPD (n= 950502; 17 studies)	Mortality (no COPD)	aOR 1.28 (1.17-1.43)	I^2= 34.5 Random effects model
Reyes et al.	Asthma & COPD	COPD (n= 18 studies)	Mortality (no COPD)	OR 2.74 (2.04-3.68)	I^2= 64.1 Random effects model
Taylor et al.	Any	Respiratory disease	Mortality (no resp disease)	OR 1.75 (1.33-2.31)	I^2=63.4

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		(n=41 studies)			Random effects model
Xiang et al.	Any	Respiratory disease (n=17 studies)	Mortality (no resp disease)	OR 2.55 (2.14-3.05)	I^2=37.2 Random effects model

Kidney disease

As with the other comorbid conditions in this review, chronic kidney disease (CKD) was very poorly defined in the literature. Two studies specified acute kidney injury (AKI) as a condition of interest (Wang, Luo, Zhang et al, 2021; Dessie & Zewotir, 2021); otherwise, CKD was used as the catch-all term.

Eleven studies were identified that analyzed the association between kidney disease and severe COVID-19 outcomes (tables 25-27). There was a consistent moderate to high strength association between kidney disease and hospitalization (table 25) and mortality (table 27), but an inconsistent association between kidney disease and ICU admission (table 26). The reason for this discrepancy is not clear, but may be related to health system or patient-level factors (such as ICU triage or goals of care) rather than biological factors.

Table 25. Association between kidney disease and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	CKD (7 studies)	Hospitalization (no CKD)	OR 5.89 (3.16-11)	I^2= 72 Random effects model
Lin et al.	CKD	Hospitalization outcome (adjusted) (n= 5810; 2 studies)	Hospitalization (no CKD)	OR 2.59 (1.92-3.51)	I^2= 0.0 Fixed effects model

Table 26. Association between kidney disease and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	CKD (n= 247681)	ICU admission (no CKD)	OR 2.25 (1.73-2.94)	I^2=82.8 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Hoang & Anh	Any	CKD	ICU admission (no CKD)	RR 1.56 (0.47 - 5.12)	I^2= 0.0 Fixed effects model
Katzenschlager et al.	Any	CKD (13 studies)	ICU admission (no CKD)	OR 1.48 (1.08-2.03)	I^2= 26.2 Random effects model

Table 27. Association between kidney disease and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	CKD	Mortality (no CKD)	RR 3.96 (2.65; 5.910	I^2= 0.0
Cai, Zhang, Zhu et al.	CKD	All studies (n= 39658)	Mortality (no CKD)	OR 5.81 (3.78–8.94)	I^2= 30% Fixed effects model
		Age ≥ 70 years (n= 84)	Mortality (no CKD)	OR 2.44 (0.75–6.63)	I^2 = 0% Fixed effects model
		Age < 70 years (n= 39574)	Mortality (no CKD)	OR 8.69 (7.56–9.97)	I^2 = 30% Fixed effects model
Dessie & Zewotir	Any	Acute Kidney Injury 5 studies	Mortality (no AKI)	pOR 1.87 (1.48–2.26)	I^2 = 86.5 Mixed effect model
Du, Wang, Li et al.	Any	CKD (n= 3952)	Mortality (no CKD)	OR 3.59 (1.90-6.76)	I^2=0% Fixed effects model
Geng et al.	Any	CKD (n= 105860)	Mortality (no CKD)	OR 2.85, (2.44–3.33)	I^2=78.3 Random effects model
Katzenschlager et al.	Any	CKD (29 studies)	Mortality (no CKD)	OR 2.36 (1.89-2.94)	I^2= 17.5 Random effects model
Lin et al.	CKD	All-cause mortality (adjusted) (n= 8465; 4 studies)	Mortality (no CKD)	OR 2.70 (2.06-3.54)	I^2= 25% Fixed effects model
Taylor et al.	Any	Kidney disease (n=28 studies)	Mortality (no kidney disease)	OR 2.39 (1.68-3.40)	I^2=69.1 Random effects model
Wang, Luo, Zhang et al.	Kidney disease	Chronic kidney disease (n= 11 studies)	Mortality (no CKD)	OR 5.11 (3.36-7.77)	I^2=0 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		Acute kidney injury (n= 6 studies)	Mortality (no AKI)	OR 30.46 (18.33-50.95)	I^2=42 Random effects model
Xiang et al.	Any	CKD (n= 9 studies)	Mortality (no CKD)	OR 1.82 (1.46-2.28)	I^2=0 Random effects model

Liver disease

Liver disease was not frequently considered as a comorbidity of interest in severe COVID-19 and was often undefined. Seven studies analyzed the association between liver disease (chronic or acute) and severe outcomes from COVID-19 (tables 28-30). Liver disease does not appear to be a risk factor for severe COVID-19 – the association with hospitalization (table 28), ICU admission (table 29) and mortality (table 30) are inconsistent and mostly statistically insignificant.

Table 28. Association between chronic liver disease and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Sharma et al.	Liver disease	Chronic liver disease (17 studies)	Hospitalization (no CLD)	OR 0.96 (0.71, 1.29)	I^2= 0 Random effects model
		Acute liver injury (4 studies)	Hospitalization (no ALI)	OR 2.98 (2.35-3.77)	I^2= 36 Random effects model

Table 29. Association between chronic liver disease and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Chronic liver disease (n= 7588)	ICU admission (no LD)	OR 1.48 (0.95-2.29)	I^2= 0 Fixed effects model
Hegyi et al.	Non-alcoholic fatty liver disease (NAFLD)	ICU admission outcome (n= 3 studies)	ICU admission (no NAFLD)	OR 2.29 (0.79-6.63)	I^2= 85.1 Random effects model
Hoang & Anh	Any	Chronic liver disease	ICU admission (no CLD)	RR 0.50 (0.12 - 2.06)	I^2= 0.0 Fixed effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	Liver disease (10 studies)	ICU admission (no LD)	OR 1.32 (0.84-2.08)	I^2= 0.0 Random effects model
Singh, Hussain & Antony	NAFLD	ICU outcome (n= 2 studies)	ICU admission (no NAFLD)	pOR 1.66 (1.26-2.20) adjusted	I^2=0 Random effects model

Table 30. Association between chronic liver disease and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Chronic liver disease (n= 36481)	Mortality (no liver disease)	OR 1.52 (1.30–1.77)	I^2=32.3 Fixed effects model
Katzenschlager et al.	Any	Liver disease (15 studies)	Mortality (no LD)	OR 1.32 (0.85-2.04)	I^2= 0.6 Random effects model
Singh, Hussain & Antony	NAFLD	Mortality outcome (n= 2 studies)	Mortality (no NAFLD)	pOR 1.01 (0.65 – 1.58) adjusted	I^2=0 Random effects model
Taylor et al.	Any	Liver disease (n= 17 studies)	Mortality (no liver disease)	OR 1.29 (0.85-1.97)	I^2=30.5 Random effects model

Cancer

Cancer was considered as a comorbidity of interest in seven included studies; however, it is not clear how meaningful or useful these associations may be. “Cancer” is not a specific term and can refer to thousands of different pathologies that might have different effects on an individual’s risk of severe COVID-19 outcomes (eg. inactive cancer, non-melanoma skin cancer vs. an immune system cancer). Across the seven studies, the associations between cancer and hospitalization (table 31), ICU admission (table 32) and mortality (table 33) are inconsistent, but weak-moderate at best.

Table 31. Association between cancer and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Katzenschlager et al.	Any	Cancer	Hospitalization (no cancer) (4 studies)	OR 1.64 (0.95-2.84)	I^2= 64 Random effects model

Table 32. Association between cancer and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Cancer (n= 25235)	ICU admission (no cancer)	OR 1.57 (1.39-1.77)	I^2= 34.2 Fixed effects model
Hoang & Anh	Any	Malignancy	ICU admission (no malignancy)	RR 2.26 (1.27 - 4.01)	I^2= 31.5 Fixed effects model
Katzenschlager et al.	Any	Cancer (14 studies)	ICU admission (no cancer)	OR 1.29 (1.02-1.64)	I^2= 9.2 Random effects model

Table 33. Association between cancer and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Cancer	Mortality (no cancer)	RR 1.60 (0.60; 4.23)	I^2=none
Dessie & Zewotir	Any	Cancer 3 studies	Mortality (no cancer)	pOR 1.43 (0.06–2.80)	I^2 = 80.0 Mixed effect model
Geng et al.	Any	Cancer (n= 169117)	Mortality (no cancer)	OR 2.11, (1.85–2.42)	I^2=70.5 Random effects model
Katzenschlager et al.	Any	Cancer (28 studies)	Mortality (no cancer)	OR 2.08 (1.55-2.77)	I^2= 40.6 Random effects model
Taylor et al.	Any	Malignancy (n= 29 studies)	Mortality (no malignancy)	OR 1.81 (1.30-2.52)	I^2=58.3 Random effects model
Xiang et al.	Any	Cancer (n= 10 studies)	Mortality (no cancer)	OR 1.43 (1.12-1.82)	I^2=22.4 Random effects model

Pregnancy

Two studies were identified that described maternal outcomes of pregnant people who are infected with COVID-19. The majority of meta-analytic studies on pregnancy and COVID-19 focused on fetal & newborn outcomes and the effect of infection on the pregnancy itself, rather than the effect of COVID-19 on the mother. These are useful outcomes that could be the subject of a separate review; however, only maternal

hospitalization, ICU admission (table 34), and mortality (table 35) were of interest in this review.

Pregnancy had a moderate to high strength association with ICU admission, but a very inconsistent association with mortality. Some interaction effects were demonstrated by La Verde et al (2021), notably for obesity. However, this is a small meta-analysis (n=2 articles) and these results may not persist as more research becomes available. This suggests that pregnancy is a risk factor for severe disease, but the relationship to mortality may be reduced because pregnant women are usually young and healthy prior to being admitted to ICU.

Table 34. Association between pregnancy and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Khan et al.	Pregnancy	ICU admission outcome (n= 424,587, 5 studies)	ICU admission (non-pregnant)	RR 2.26 (1.68-3.05)	n/a
La Verde et al.	Pregnancy	ICU admission outcome (n= 1281)	ICU admission (non-pregnant)	RR 5.09 (2.00-12.98)	I^2= 56% Random effects model

Table 35. Association between pregnancy and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Khan et al.	Pregnancy	Mortality outcome	Mortality (non-pregnant)	RR 1.08 (0.89-1.31)	n/a
La Verde et al.	Pregnancy	Pregnancy * ≥ 1 comorbidity (n= 1281)	Mortality (no comorb)	RR 2.26 (1.77-2.89)	I^2= 76% Random effects model
		Pregnancy * Gestational Diabetes (n= 1281)	Mortality (no diabetes)	RR 5.71 (0.77-42.44)	I^2= 94% Random effects model
		Pregnancy * Obesity (n= 1281)	Mortality (non-obese)	RR 2.48 (1.41-4.26)	I^2=0% Random effects model
		Pregnancy * Asthma (n= 1281)	Mortality (no asthma)	RR 2.05 (0.81 – 5.15)	I^2= 0% Random effects model

Cerebrovascular disease

Five articles were identified that considered the association of cerebrovascular disease (CeVD) and severe outcomes from COVID-19 (tables X36 and 37). The strength of associations were inconsistent, however, on balance the evidence suggests that individuals with cerebrovascular disease have moderately increased odds of ICU admission (table 36) and mortality (table 37) from COVID-19.

Notably, cerebrovascular disease was not defined at all in the literature, which limits the usefulness of these association measures. CeVD generally refers to stroke; however, the underlying pathology and mechanism of action is heterogeneous (Good et al., 1990) and may interact in different ways with SARS-CoV-2.

Table 36. Association between cerebrovascular disease and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Cerebrovascular disease (n= 23544)	ICU admission (no CeVD)	OR 1.66 (1.00-2.75) p=0.48	I^2= 80.7 Random effects model
Katzenschlager et al.	Any	Cerebrovascular disease (7 studies)	ICU admission (no CeVD)	OR 5.88 (2.35-14.73)	I^2= 16.3 Random effects model
Patel et al.	CeVD	ICU outcome Age adjusted	ICU admission (no CeVD)	OR: 1.82 (1.25–2.69)	I^2= 93.4 Random effects model
Siepmann et al.	CeVD	ICU outcome (n= 3 studies)	ICU admission (no CeVD)	RR 2.79 (1.83-4.24)	I^2= 35.3 Random effects model

Table 37. Association between cerebrovascular disease and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Cerebrovascular disease (n= 139221)	Mortality (no CeVD)	OR 2.46 (2.08–2.91)	I^2=69.7 Random effects model
Katzenschlager et al.	Any	Cerebrovascular disease (20 studies)	Mortality (no CeVD)	OR 3.45 (2.42-4.91)	I^2= 24.5 Random effects model
Patel et al.	CeVD	Mortality outcome Age adjusted	Mortality (no CeVD)	OR 1.42 (1.14–1.77)	I^2= 96.1 Random effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Siepmann et al.	CeVD	Mortality outcome (n= 6 studies)	Mortality (no CeVD)	RR 2.18 (1.75-2.70)	I^2=13.2 Random effects model
Taylor et al.	Any	Cerebrovascular disease (n= 12 studies)	Mortality (no CeVD)	OR 1.61 (0.92-2.83)	I^2=57.2 Random effects model

Major Organ Transplant

Three articles were identified that analyzed the effect of heart, kidney, and liver transplantation on COVID-19 mortality (table 38). In general, receiving a transplant was very inconsistently associated with mortality from COVID-19 and in most cases, not significant. Interaction effects were identified with age, diabetes, and stage 3 CKD that resulted in high-strength association with mortality. The reason for this pattern of risk is unclear.

Table 38. Association between past organ transplant and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Bachul et al.	Kidney transplant recipients	Age ≥ 60 years	Mortality (Age <60 years)	OR 3.90 (2.56, 5.94)	I^2 = 0% Random effects model
		Time since transplant ≥ 2 years	Mortality (< 2 years post-transplant)	OR 1.37 (0.72, 2.58)	I^2 = 0% Random effects model
		Gender (male)	Mortality (female)	OR 0.71 (0.50–1.01)	I^2 = 0% Random effects model
Granger et al.	Heart transplant	HT * Pre-existing diabetes mellitus (n= 120)	Mortality (no DM)	OR 3.60, (1.43–9.06)	I^2= 0.0 Fixed effects model
		HT * CKD Stage III+ (n= 100)	Mortality (no CKD)	OR 3.79 (1.39–10.31)	I^2= 0.0 Fixed effects model
		HT * Male sex (n=121)	Mortality (female)	OR 2.26 (0.89-6.67)	I^2= 0.0 Fixed effects model
		HT * Pre-existing HTN (n= 121)	Mortality (no HTN)	OR 0.78 (0.33-1.85)	I^2= 0.0 Fixed effects model
		HT * ACEI/ARB (n= 62)	Mortality (No ACEI/ARB therapy)	OR 1.09 (0.34-3.48)	I^2= 0.0 Fixed effects model
		HT * Single or dual immunosuppressive therapy	Mortality (triple or quadruple immunosuppression)	OR 2.65 (0.62-11.37)	I^2= 0.0 Fixed effects model

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
		(n= 66)			
Jayant et al.	Liver transplant	Age ≥ 60-65 years	Mortality (Age < 60-65 years)	OR 4.26 (2.14-8.49)	I^2 = 0.0 Random effects model
		> 2 years post-transplant	Mortality (≤ 2 years post-transplant)	OR 3.07 (0.65-14.46)	I^2 = 0.0 Random effects model
		Female	Mortality (male)	OR 1.05 (0.62-1.80)	I^2 = 0.0 Random effects model

Immunosuppression

No studies were identified that directly analyzed the risk of severe outcomes from COVID-19 in immunosuppressed populations. Three included studies identified immunosuppression or immunodeficiency as a subgroup for either mortality (three studies) or ICU admission (one study). Immunodeficiency was not identified as a significant risk of severe COVID-19 outcomes in any analyses.

Table 39. Association between cerebrovascular disease and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	"Immunodeficiencies"	Mortality (no Immunodeficiency)	RR 5.28 (0.26; 108.12)	Not presented
Granger et al.	Heart Transplant	HT * Single or dual immunosuppressive therapy (n= 66)	Mortality (triple or quadruple immunosuppression)	OR 2.65(0.62-11.37)	I^2= 0.0 Fixed effects model
Katzenschlager et al.	Any	Immunosuppressive therapy	ICU admission (no immunosuppression) (5 studies)	OR 0.78 (0.34-1.77)	I^2= 7.1 Random effects model
			Mortality (no immunosuppression) (5 studies)	OR 1.33 (0.62-2.86)	I^2= 48.2 Random effects model

Other Conditions

Various other comorbidities or factors were identified in the literature as one-offs. These are included below according to outcome: hospitalization (table 39), ICU admission (table 40), and mortality (table 41). Three patterns are identifiable:

- Hyperlipidemia / hypercholesterolemia has an inconsistent but significant association with severe outcomes from COVID-19 (two articles). This may be confounded by obesity and CVD.

- Obstructive sleep apnea has a consistent, moderate-strength association with ICU admission and mortality from COVID-19 (two articles). This may be confounded by age, obesity and pulmonary disease.
- Hip fracture appears to have a high-strength association with COVID-19 mortality, however, this may be a confounded relationship with age and frailty (two studies).

Table 40. Association between other conditions and COVID-19 hospitalization. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Associations that appear to be protective are not shaded. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Aminian & Tu	Prior bariatric surgery	Hospital admission (n=736)	Hospitalization (no prior bariatric surgery)	OR 0.28 (0.12–0.65)	I^2 = 0% Random effects model
Ceban et al.	Mood disorders	Hospitalization outcome (n= 26554397)	Hospitalization (no mood disorder)	OR 1.31 (1.12-1.53)	I^2= 98.5% Random effects model
Singh, Jena, Kumar et al.	Inflammatory bowel disease	Ulcerative colitis	Hospitalization (Crohn's disease) (n= 2201)	RR 1.55 (1.22-1.97)	I^2=15 Random effects model

Table 41. Association between other conditions and ICU admission or mechanical ventilation for COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Geng et al.	Any	Hyperlipidemia (n= 13067)	ICU admission (no HL)	OR 1.53 (1.22-1.93)	I^2=53.2 Random effects model
		Any chronic disease (n=231605)	ICU Admission	OR 2.82 (2.23-3.56)	I^2= 81.0 Random effects model
Hariyanto & Kurniawan (2021a)	Obstructive sleep apnea	ICU outcome (n= 11 studies)	ICU admission (no OSA)	OR 1.76 (1.51-2.05)	I^2= 0.0 Random effects model
Singh, Jena, Kumar et al.	Inflammatory bowel disease	Ulcerative colitis (n=2016)	ICU admission (Crohn's disease)	RR 1.42 (0.97-2.07)	I^2=0 Random effects model

Table 42. Association between other conditions and mortality from COVID-19. Low strength associations (n.s., OR <1.67 or HR/RR <1.5) are shaded green; moderate strength associations (OR 1.68-3.47; HR/RR 1.5-2.5) are shaded yellow; and high strength associations (OR>3.47 or HR/RR >2.5) are shaded red. Associations that are not statistically significant are shaded in grey. Associations that appear to be protective are not shaded. Measures of association are univariate unless otherwise listed.

Reference	Population	Subgroup	Outcome (reference)	Association	Heterogeneity (I^2 statistic)
Alves et al.	Italians ≥ 65	Immunodeficiency	Mortality (no immunodeficiency)	RR 5.28 (0.26; 108.12)	I^2= none
		Metabolic disease	Mortality (no metabolic disease)	RR 1.51 (0.60; 3.75)	I^2= none
		Familial hypercholesterolemia	Mortality (no FH)	RR 3.27 (2.49; 4.29)	I^2=none
		Dementia	Mortality (no dementia)	RR 3.67 (2.43; 5.55)	I^2= none
Aminian & Tu	Prior bariatric surgery	All studies (n=9022)	Mortality (no prior bariatric surgery)	OR 0.22 (0.19–0.26)	I^2 = 0% Random effects model
Ceban et al.	Mood disorders	Mortality outcome (n= 25 808 660)	Mortality (no mood disorder)	OR 1.51 (1.34-1.69)	I^2= 67.2% Random effects model
Geng et al.	Any	Hyperlipidemia	Mortality (no hyperlipidemia) (n= 79205)	OR 1.72, (1.07–2.77)	I^2= 97.8 Random effects model
		Any chronic disease	Mortality (no chronic disease) (n=148907)	OR 3.11 (2.64-3.65)	I^2= 88.8 Random effects model
Hariyanto & Kurniawan (2021a)	Obstructive sleep apnea	Mortality outcome (n= 12 studies)	Mortality (no OSA)	OR 1.74 (1.39–2.19)	I^2= 48% Random effects model
Katzenschlager et al.	Any	Digestive system disease	Mortality (no GI disease) (5 studies)	OR 1.67 (0.81-3.45)	I^2= 0.0 Random effects model
Kumar et al.	Fractures	Hip fracture (n= 61)	Mortality (non-hip fractures)	OR 9.76 (1.26-75.72)	I^2= 46% Fixed effects model
		Lower limb fracture (n= 59)	Mortality (upper limb fracture)	OR 2.94 (0.25- 33.9)	Fixed effects model
Liang, Luo, Chen et al.	HIV+	Mortality outcome (6 studies)	Mortality (no HIV)	RR 0.96 (0.88-1.06)	I^2= 0% Random effects model
Lim & Pranata	Hip fracture	Mortality outcome (4 studies)	Mortality (no hip fracture)	RR 7.45 [2.72, 20.43]	I^2= 68.6% Random effects model
Putri et al.	Parkinson's disease	Mortality outcome (n= 6 studies)	Mortality (no Parkinson's)	OR 2.62 (1.50-4.60)	I^2= 91 Random effects model
Singh, Jena, Kumar et al.	Inflammatory bowel disease	Ulcerative colitis	Mortality (Crohn's disease) (n= 2094)	RR 1.94 (1.22-3.10)	I^2=0 Random effects model

Medications

Fifteen articles were identified that described the effect of different medication therapies for common chronic diseases on COVID-19 hospitalization (table 42), ICU admission

(table 43) and mortality (table 44). Commonly under investigation were angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) for cardiovascular disease (4 studies); dipeptidyl peptidase-4 (DPP-4) inhibitors for diabetes (5 studies); insulin treatment (two studies); and statins (two studies). One study each was identified that examined calcium channel blockers, proton pump inhibitors and anti-retroviral therapy (ART).

These studies and analyses are included in the evidence extraction table (Appendix B), however, the findings are biologically implausible and may be heavily confounded by other medications and comorbid conditions. The utility of this information is limited at best and this has not been compiled into tables.

Evolving Evidence

A retrospective cohort study of risk factors for severe disease based on data from Alberta was recently submitted to PLOS-One for publication (personal communication). The results of this study, which is based on a cohort of 13,167 COVID-19 cases that received hospital care between March and August 2020, suggest that the risk factors for severe COVID-19 outcomes in Alberta are not different from those in other jurisdictions (Saini et al., unpublished). When the Alberta study has been accepted for publication, it may be useful to compare and integrate the Alberta-specific data into this analysis.

Appendices

A. List of Abbreviations

ACE2: Angiotensin Converting Enzyme-2

ACEI: angiotensin converting enzyme inhibitors

AHS: Alberta Health Services

AKI: Acute Kidney Injury

ALI: Acute Liver Injury

ARB: angiotensin receptor blockers

ART: Anti-retroviral therapy

BMI: Body Mass Index

CAD: Coronary Artery Disease

CHD: Coronary Heart Disease

CKD: Chronic Kidney Disease

CLD: Chronic Liver Disease

COPD: Chronic Obstructive Pulmonary Disease

COVID-19: Coronavirus Disease 2019

CVD: Cardiovascular disease

DPP-4: dipeptidyl peptidase-4

HF: Heart Failure

HIV: Human Immunodeficiency Virus

HR: Hazard Ratio

HTN: Hypertension

ICU: Intensive Care Unit

MV: Mechanical Ventilation

OR: Odds Ratio

pOR: pooled odds ratio

RR: Risk Ratio

SAG: Scientific Advisory Group

B. Evidence Extraction Tables

Table 43. Evidence extracted from each included study

Note: All references were published in 2021

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
Alsagaff et al.	SR & MA Any observational study January – October 2020 N= 31 studies	Calcium channel blocker use	All studies (n=82095)	Mortality (no CCB use)	OR 1.21 [0.98,1.49]	I^2= 84% Mantel-Haenszel Random Effects Effect is maintained in sensitivity analysis
				Mechanical Ventilation (no CCB use)	OR 0.97 [95%CI: 0.47 to 2.00]	I^2 = 76% M-H Random Effects model Effect is maintained in sensitivity analysis
			Hypertensive patients (n=11548)	Mortality (no CCB use)	OR 0.69 [0.52,0.91]	I^2= 62% M-H Random Effects Model Effect is maintained in sensitivity analysis
				Mechanical Ventilation (no CCB use)	(OR = 0.71 [95%CI: 0.29 to 1.76]	I^2= 84% M-H Random Effects Model Effect is maintained in sensitivity analysis
Alves et al.	SR & MA Any article type July 2020 N= 5 studies	Italians ≥ 65 years old	Male	Mortality (female)	RR 0.98 (0.67; 1.43)	I^2= 89.3
			Chronic Diseases	Mortality (no chronic disease)	RR 1.20 (0.94,1.54)	I^2= none
			Cancer	Mortality (no cancer)	RR 1.60 (0.60; 4.23)	I^2=none
			Diabetes	Mortality (no diabetes)	RR 1.90 (1.53; 2.37)	I^2= 62.7
			Cardiovascular diseases/coronary artery disease	Mortality (no CVD)	RR 1.80 (0.85; 3.80)	I^2= 92.0
			COPD	Mortality (no COPD)	RR 2.19 (1.54; 3.10)	I^2= 0.0
			Immunodeficiencies	Mortality (no immunodeficiencies)	RR 5.28 (0.26; 108.12)	I^2= none
			Chronic Kidney Disease	Mortality (no CKD)	RR 3.96 (2.65; 5.910	I^2= 0.0
			Metabolic disease	Mortality (no metabolic disease)	RR 1.51 (0.60; 3.75)	I^2= none
			Obesity (no definition)	Mortality (no obesity)	RR 1.28 (0.78; 2.10)	I^2= 60.8
			Hypertension	Mortality (no hypertension)	RR 1.37 (1.24, 1.51)	I^2= 69.3
			Familial hypercholesterolemia	Mortality (no FH)	RR 3.27 (2.49; 4.29)	I^2=none
			Dementia	Mortality (no dementia)	RR 3.67 (2.43; 5.55)	I^2= none
			Smoking	Mortality (no smoking)	RR 0.74 (0.32; 1.71)	I^2= none

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
Aminian & Tu	SR & MA Any article type January-November 2020 N= 3 articles	Prior bariatric surgery	All studies (n=9022)	Mortality (no prior bariatric surgery)	OR 0.22 (0.19–0.26)	I^2 = 0% Random effects model
			Hospital admission (n=736)	Hospitalization (no prior bariatric surgery)	OR 0.28 (0.12–0.65)	I^2 = 0% Random effects model
Bachul et al.	SR & MA Retrospective observational studies and case series November 2020; April 2021 N= 48 articles	Kidney transplant recipients (n= 3137 patients)	Age ≥ 60 years	Mortality (Age <60 years)	OR 3.90 (2.56, 5.94)	I^2 = 0% Random effects model
			Time since transplant ≥ 2 years	Mortality (< 2 years post-transplant)	OR 1.37 (0.72, 2.58)	I^2 = 0% Random effects model
			Gender (male)	Mortality (female)	OR 0.71 (0.50–1.01)	I^2 = 0% Random effects model
Bae et al.	SR & MA Observational studies (case series & cohort) Search to June 2020 N= 51 articles	Risk factors for cardiovascular disease (CVD) or CVD (n= 48317 patients)	Hypertension * Age < 50 (n= 6143)	Mortality (no hypertension)	OR 6.13 (4.01; 9.39)	Random effects model
			Hypertension * Age 50-60 (n= 13111)	Mortality (no hypertension)	OR 2.81 (1.97; 4.01)	Random effects model
			Hypertension * Age ≥ 60 (n= 10180)	Mortality (no hypertension)	OR 2.10 (1.67; 2.64)	Random effects model
			Diabetes * Age < 50 (n= 6026)	Mortality (no diabetes)	OR 5.31 (3.22; 8.26)	Random effects model
			Diabetes * Age 50-60 (n= 9965)	Mortality (no diabetes)	OR 2.22 (1.82; 2.72)	Random effects model
			Diabetes * Age ≥ 60 (n= 27513)	Mortality (no diabetes)	OR 1.76 (1.27; 2.44)	Random effects model
			CVD * Age < 50 (n= 5838)	Mortality (no CVD)	OR 7.80 (4.06; 15.00)	Random effects model
			CVD * Age 50-60 (n= 6124)	Mortality (no CVD)	OR 3.14 (1.12; 8.78)	Random effects model
			CVD * Age ≥ 60 (n= 24599)	Mortality (no CVD)	OR 2.46 (1.91; 3.17)	Random effects model
Cai, Yang & Zhang	SR & MA Observational studies (no case reports) Search to January 2021 N= 46 articles	Obesity	Hospitalization outcome (n= 396603)	Hospitalization (non-obese)	OR 1.72, (1.55-1.92)	I^2= 47.4% Fixed effects model
			Mechanical ventilation outcome (n=2088)	MV (non-obese)	OR 1.66, (1.42–1.94)	I^2= 41.3% Fixed effects model
			Mortality outcome (n= 29305)	Mortality (non-obese)	OR 1.61, (1.29–2.01)	I^2= 83.1% Random effects model
Cai, Zhang, Zhu et al.	SR & MA Case reports excluded Search to May 2020 N= 12 articles	Chronic kidney disease	All studies (n= 39658)	Mortality (no CKD)	OR 5.81 (3.78–8.94)	I^2= 30% Fixed effects model
			Age ≥ 70 years (n= 84)	Mortality (no CKD)	OR 2.44 (0.75–6.63)	I^2 = 0% Fixed effects model
			Age < 70 years (n= 39574)	Mortality (no CKD)	OR 8.69 (7.56–9.97)	I^2 = 30% (2% after removing Chen & Wang) Fixed effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
Ceban et al.	SR & MA Observational studies Search to February 2021 N= 21 articles	Mood disorders (DSM-5 diagnosis of depression or bipolar disorder)	Hospitalization outcome (n= 26 554 397)	Hospitalization (no mood disorder)	OR 1.31 (1.12-1.53)	I^2= 98.5% Random effects model
			Mortality outcome (n= 25 808 660)	Mortality (no mood disorder)	OR 1.51 (1.34-1.69)	I^2= 67.2% Random effects model
Corona et al.	SR & MA Observational studies Search to July 2020 N= 87 articles	Any	Diabetes mellitus (20 included studies)	Mortality (no diabetes)	OR 1.85 (1.36 – 2.51)	I^2= 95.3% Random effects model
Dai et al.	SR & MA Observational studies Search to June 2020 N= 42 articles	Renin-Angiotensin System inhibitors (ACEI/ARBs)	Peer-reviewed data *no subgroup differences in preprints	Mortality (no ACEI/ARBs)	OR 0.87 (0.71, 1.06)	I^2= 58% Random effects model
Deng et al.	SR & MA Observational studies Search to June 2020 N= 11 articles	Obesity [MA includes "severe COVID" outcome that shows a significant effect]	All studies (n= 5175)	Mortality (non-obese)	OR 1.05 (0.65–1.71)	I^2= 66.6% Random effects model
			Per 5 kg/m^2 in BMI (dose response)	Mortality	OR 0.96 (0.83–1.11)	
Dessie & Zewotir	SR & MA Observational studies Search to August 2020 N= 42 articles	Any	Older Age (undefined) 21 studies	Mortality (younger age)	pOR 2.61 (1.75–3.47)	I^2= 99.9 Mixed effect model
			Male gender 15 studies	Mortality (female)	pOR 1.45 (1.41–1.51)	I^2= 66.7 Mixed effect model
			Smoking 5 studies	Mortality (no smoking)	pOR 1.42 (1.01–1.83)	I^2= 55.8 Mixed effect model
			Obesity 9 studies	Mortality (non-obese)	pOR 1.34 (1.17–1.52)	I^2= 82.6 Mixed effect model
			CVD 9 studies	Mortality (no CVD)	pOR 1.83 (1.50–2.17)	I^2= 41.27 Mixed effect model
			Diabetes 13 studies	Mortality (no diabetes)	pOR 1.52 (1.36–1.69)	I^2= 79.83 Mixed effect model
			Hypertension 12 studies	Mortality (no hypertension)	pOR 1.57 (1.27–1.87)	I^2 = 94.9 Mixed effect model
			COPD 7 studies	Mortality (no COPD)	pOR 1.58 (1.08–2.07)	I^2 = 92.2 Mixed effect model
			Cancer 3 studies	Mortality (no cancer)	pOR 1.43 (0.06–2.80)	I^2 = 80.0 Mixed effect model
			Acute Kidney Injury 5 studies	Mortality (no AKI)	pOR 1.87 (1.48–2.26)	I^2 = 86.5 Mixed effect model
			Cardiac Injury 3 studies	Mortality (no cardiac injury)	pOR 2.33 (0.88–3.79)	I^2= 6.0 Mixed effect model
Du, Zhou, Zha et al.	SR & MA Observational studies Search to November 2020	Hypertension	Mortality outcome (multivariate analysis) (n= 7212)	Mortality (no hypertension)	OR 2.17; (1.67–2.82)	I^2= 67.3 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
	N= 24 articles		Mortality outcome (no adjustment)	Mortality (no hypertension)	OR 2.59 (1.91–3.51)	I^2= 53.2 Random effects model
			Age > 60 years	Mortality (HTN * Age ≤ 60)	OR: 3.12 (1.93 − 5.05)	I^2= 59.8 Random effects model
Du, Lv, Zha et al.	SR & MA Observational studies (case reports excluded) Search to August 2020 N= 16 articles	Increasing BMI Obesity = BMI ≥30 kg/m^2 BMI >35 kg/m^2 vs. 30-35 kg/m^2	BMI ≥ 30 (n= 14124)	Mortality (non-obese)	OR 2.68 (1.65–4.37)	I^2= 79.3 Random effects model
			Age > 60 years	Mortality (Obese * Age ≤ 60)	OR 3.93, (2.18–7.09)	I^2= 48.6
			BMI ≥ 35	Mortality (BMI 30-35)	OR 3.54 (1.48–8.48)	I^2= 72
			Multivariate analysis	Mortality (non-obese)	pOR 3.34 (1.89–5.90	I^2= 78.4
			1 kg/m^2 BMI increase above 18	Mortality	OR 1.06, (1.02–1.10)	
Du, Wang, Li et al.	SR & MA Any study type Search to Oct 2020 N= 17 articles	Any	Age ≥ 60 years (n=1168)	Mortality (age < 60)	OR 6.00 (3.48–10.34)	I2 = 31% Fixed effects model
			Male gender (n=302)	Mortality (female)	OR 1.54 (1.13-2.10)	I^2= 10% Fixed effects model
			Chronic lung disease (n=4694)	Mortality (no lung disease)	OR 3.72 (2.00–6.94)	I^2= 61% Random effects model
			Diabetes (n=4873)	Mortality (no diabetes)	OR 2.60 (2.03–3.34)	I^2= 9% Fixed effects model
			Hypertension (n=4158)	Mortality (no hypertension)	OR 3.53 (2.49-5.01)	I^2=51% Random effects model
			CKD (n= 3952)	Mortality (no CKD)	OR 3.59 (1.90-6.76)	I^2=0% Fixed effects model
			CVD (n=4873	Mortality (no CVD)	OR 4.91 (3.28,7.35)	I^2=44% Fixed effects model
Geng et al.	SR & MA Any study type Search to December 2020 N= 217 articles	Any	Hypertension	Mortality (no HTN) (n= 254926)	OR 2.31 (2.04–2.61)	I^2= 92.2 Random effects model
				ICU Admission (no HTN) (n= 259220)	OR 2.24 (1.90-2.63)	I^2 = 87.1 Random effects model
			Diabetes	Mortality (no diabetes) (n=307588)	OR 1.99 (1.82–2.18)	I^2= 84.8 Random effects model
				ICU Admission (no diabetes) (n= 259522)	OR 2.50 (2.18-2.87)	I^2= 79.6 Random effects model
			COPD	Mortality (no COPD) (n= 65928)	OR 2.95 (2.48–3.50)	I^2=73 Random effects model
				ICU Admission (no COPD) (n=231641)	OR 2.76 (1.99-3.82)	I^2=69.7 Random effects model
			Asthma	Mortality (no asthma) (n= 47470)	OR 0.74 (0.68-0.80)	I^2= 0 Fixed effects model
				ICU admission (no asthma) (n=227500)	OR 1.07 (0.94-1.22)	I^2=26.1 Fixed effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
			Unspecified pulmonary disease	Mortality (no lung disease) (n= 140960)	OR 2.05 (1.83–2.31)	I^2=63.1 Random effects model
				ICU admission (no lung disease) (n= 20752)	OR 1.40 (1.26-1.56)	I^2= 0 Fixed effects model
			Coronary heart disease	Mortality (no CHD) (n= 46130)	OR 2.46, (2.14–2.82)	I^2= 63.1 Random effects model
				ICU admission (no CHD) (n= 22459)	OR 2.16 (1.56-2.99)	I^2=79.9 Random effects model
			Heart failure	Mortality (no HF) (n= 143780)	OR 2.74, (2.21–3.40)	I^2= 92.9 Random effects model
				ICU admission (no HF) (n= 28505)	OR 1.80 (1.44-2.25)	I^2= 62.7 Random effects model
			Unspecified CVD	Mortality (no CVD) (n= 68579)	OR 2.59, (2.24–3.00)	I^2= 79.3 Random effects model
				ICU admission (no CVD) (n= 220351)	OR 2.38 (1.92-2.96)	I^2= 54.8 Random effects model
			Cerebrovascular disease	Mortality (no stroke) (n= 139221)	OR 2.46 (2.08–2.91)	I^2=69.7 Random effects model
				ICU admission (no stroke) (n= 23544)	OR 1.66 (1.00-2.75) p=0.48	I^2= 80.7 Random effects model
			Hyperlipidemia	Mortality (no hyperlipidemia) (n= 79205)	OR 1.72, (1.07–2.77)	I^2= 97.8 Random effects model
				ICU admission (no HL) (n= 13067)	OR 1.53 (1.22-1.93)	I^2=53.2 Random effects model
			Obesity	Mortality (no obesity) (n= 155450)	OR 1.19, (0.94–1.51)	I^2= 93.0 Random effects model
				ICU admission (no obesity) (n= 242584)	OR 1.86 (1.49-2.31)	I^2=89.4 Random effects model
			Morbid obesity (BMI ≥40)	Mortality (obesity) (n= 5531)	OR 0.98, (0.80–1.20)	I^2=0.0 Fixed effects model
			Chronic liver disease	Mortality (no liver disease) (n= 36481)	OR 1.52 (1.30–1.77)	I^2=32.3 Fixed effects model
				ICU admission (no LD) (n= 7588)	OR 1.48 (0.95-2.29)	I^2= 0 Fixed effects model
			Chronic renal disease	Mortality (no renal disease) (n= 105860)	OR 2.85, (2.44–3.33)	I^2=78.3 Random effects model
				ICU admission (no CRD) (n= 247681)	OR 2.25 (1.73-2.94)	I^2=82.8 Random effects model
			Cancer	Mortality (no cancer) (n= 169117)	OR 2.11, (1.85–2.42)	I^2=70.5 Random effects model
				ICU admission (no cancer) (n= 25235)	OR 1.57 (1.39-1.77)	I^2= 34.2 Fixed effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
			Any chronic disease	Mortality (no chronic disease) (n=148907)	OR 3.11 (2.64-3.65)	I^2= 88.8 Random effects model
				ICU Admission (n=231605)	OR 2.82 (2.23-3.56)	I^2= 81.0 Random effects model
Gerayeli et al.	SR & MA Any study type Search to January 2021 N= 39 articles	Chronic obstructive pulmonary disease (COPD)	Hospitalization outcome (n= 350509)	Hospitalization (no COPD)	pOR 4.23 (3.65-4.90)	I^2= 27.3% Fixed effects model
			ICU outcome (n= 14549)	ICU admission (no COPD)	pOR 1.35 (1.02-1.78)	I^2= 41% Fixed effects model
			Mortality outcome (n=40457)	Mortality (no COPD)	pOR 2.47 (2.18-2.79)	I^2= 12.3% Fixed effects model
Granger et al.	Cohort study & MA Observational studies Search to December 2020 N= 4 articles	Heart transplant	HT * Pre-existing diabetes mellitus (n= 120)	Mortality (no DM)	OR 3.60, (1.43–9.06)	I^2= 0.0 Fixed effects model
			HT * CKD Stage III+ (n= 100)	Mortality (no CKD)	OR 3.79 (1.39–10.31)	I^2= 0.0 Fixed effects model
			HT * Male gender (n=121)	Mortality (female)	OR 2.26 (0.89-6.67)	I^2= 0.0 Fixed effects model
			HT * Pre-existing HTN (n= 121)	Mortality (no HTN)	OR 0.78 (0.33-1.85)	I^2= 0.0 Fixed effects model
			HT * ACEI/ARB (n= 62)	Mortality (No ACEI/ARB therapy)	OR 1.09 (0.34-3.48)	I^2= 0.0 Fixed effects model
			HT * Single or dual immunosuppressive therapy (n= 66)	Mortality (triple or quadruple immunosuppression)	OR 2.65(0.62-11.37)	I^2= 0.0 Fixed effects model
Hariyanto & Kurniawan (2021a)	SR & MA Any study type Search to December 2020 N= 21 articles	Obstructive sleep apnea	ICU outcome (n= 11 studies)	ICU admission (no OSA)	OR 1.76 (1.51-2.05)	I^2= 0.0 Random effects model
			Mortality outcome (n= 12 studies)	Mortality (no OSA)	OR 1.74 (1.39–2.19)	I^2= 48% Random effects model
Hariyanto & Kurniawan (2021b)	SR & MA Any study type Search to November 2020 N= 10 articles	Dipeptidyl peptidase 4 (DPP4) inhibitor for diabetes management	Mortality outcome (n= 7 studies)	Mortality (no DPP4)	OR 1.14 (0.87-1.51)	I^2= 0% Random effects model
Hegyi et al.	SR & MA Cohort or case control Search to September 2020 N = 7 articles	Non-alcoholic fatty liver disease (NAFLD)	ICU admission outcome (n= 3 studies)	ICU admission (no NAFLD)	OR 2.29 (0.79-6.63)	I^2= 85.1 Random effects model
Helvaci et al.	SR & MA Cohort & cross-sectional studies Search to June 2020	Obesity (BMI ≥ 30)	Hospitalization outcome (n= 6952)	Hospitalization (BMI <30)	OR 1.3 (1.00-1.69) p=0.05	I^2= 52% Random effects model
			ICU Admission outcome (n= 7038)	ICU admission (BMI <30)	OR 1.51 (1.16-1.97)	I^2= 72% Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
	N= 19 articles		Mortality outcome (n=9211)	Mortality (BMI <30)	OR 1.28 (0.76-2.16)	I^2= 80% Random effects model
Hessami et al.	SR & MA Observational studies (no case reports) Search to May 2020 N= 54 (primary outcomes)	Cardiovascular disease	Acute cardiac injury (n= 12 studies)	Mortality (no ACI)	pOR 13.29 (7.35, 24.03)	I^2= 74.3 Random effects model
			Heart failure (n= 8 studies)	Mortality (no HF)	pOR 6.72 (3.34, 13.52)	I^2= 86.8 Random effects model
			Arrhythmia (n= 3 studies)	Mortality (no arrhythmia)	pOR 2.75 (1.43, 5.25)	I^2= 0 Fixed effects model
			Hypertension (n= 31 studies)	Mortality (no HTN)	pOR 2.60 (2.11, 3.19)	I^2= 73.9 Random effects model
			Cardiovascular disease (n= 14 studies)	Mortality (no CVD)	pOR 2.61 (1.89, 3.62)	I^2= 55.5 Random effects model
			Coronary heart disease (n= 16 studies)	Mortality (no CHD)	pOR 3.78 (2.42, 5.90)	I^2= 76.2 Random effects model
Hoang & Anh	Network MA Any study type Search to April 2020 N= 18 articles	Any	COPD	ICU admission (no COPD)	RR 4.76 (2.44 - 9.27)	I^2= 0.0 Fixed effects model
			Cardiovascular disease	ICU admission (no CVD)	RR 2.59 (1.61 - 4.16)	I^2= 0.0 Fixed effects model
			Hypertension	ICU admission (no HTN)	RR 2.64 (2.03 - 3.44)	I^2= 1.9 Fixed effects model
			Diabetes	ICU admission (no diabetes)	RR 2.44 (1.66 - 3.60)	I^2= 44.5 Fixed effects model
			Chronic liver disease	ICU admission (no CLD)	RR 0.50 (0.12 - 2.06)	I^2= 0.0 Fixed effects model
			Chronic kidney disease	ICU admission (no CKD)	RR 1.56 (0.47 - 5.12)	I^2= 0.0 Fixed effects model
			Malignancy	ICU admission (no malignancy)	RR 2.26 (1.27 - 4.01)	I^2= 31.5 Fixed effects model
Hoong et al.	SR & MA Controlled observational studies Search to June 2020 N= 20 studies	Obesity (BMI ≥30)	Mortality outcome (n=17322)	Mortality (BMI <30)	pOR 1.51 (1.13–2.21)	I^2= 46.2 Fixed effects model Adjusted for age, sex, and major comorbidities
Jayant et al.	SR & MA Observational studies Search to November 2020 N=12 articles	Liver transplant	Age ≥ 60-65 years	Mortality (Age < 60-65 years)	OR 4.26 (2.14-8.49)	I^2 = 0.0 Random effects model
			> 2 years post-transplant	Mortality (≤ 2 years post-transplant)	OR 3.07 (0.65-14.46)	I^2 = 0.0 Random effects model
			Female	Mortality (male)	OR 1.05 (0.62-1.80)	I^2 = 0.0 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
Kaminska et al.	SR & MA Any study type (exclude case reports) Search to December 2020 N= 19 articles	Diabetes mellitus	Mortality outcome (n= 6031)	Mortality (no DM)	OR 2.39 (1.65-3.46)	I^2= 62% Random effects model
Kandil et al.	SR & MA Observational study Search to May 2020 N= 15 articles	Diabetes mellitus	All studies (n= 75200)	Mortality (no DM)	pOR 1.87 (1.51–2.31)	I^2= 77.9%
Katzenschlager et al.	SR & MA Cross-sectional studies, cohort studies, controlled trials Search to May 2020 N= 88 articles	Any	Hypertension	Hospitalization (no HTN) (9 studies)	OR 3.28 (2.21-4.87)	I^2= 80.6 Random effects model
				ICU admission (no HTN) (22 studies)	OR 1.62 (1.24-2.12)	I^2= 69.1 Random effects model
				Mortality (no HTN) (55 studies)	OR 2.49 (2.11-2.94)	I^2= 69.4 Random effects model
			Cardiovascular disease	Hospitalization (no CVD) (6 studies)	OR 3.85 (2.56-5.81)	I^2= 75.4 Random effects model
				ICU admission (no CVD) (17 studies)	OR 1.50 (0.99-2.28)	I^2= 78.0 Random effects model
				Mortality (no CVD) (36 studies)	OR 3.93 (2.91-5.30)	I^2= 73.3 Random effects model
			Cerebrovascular disease	ICU admission (no stroke) (7 studies)	OR 5.88 (2.35-14.73)	I^2= 16.3 Random effects model
				Mortality (no stroke) (20 studies)	OR 3.45 (2.42-4.91)	I^2= 24.5 Random effects model
			COPD	ICU admission (no COPD) (12 studies)	OR 1.39 (0.90-2.16)	I^2= Random effects model
				Mortality (no COPD) (12 studies)	OR 2.54 (1.87-3.44)	I^2= 39.4 Random effects model
			Asthma	Mortality (no asthma) (4 studies)	OR 0.88 (0.58-1.35)	I^2= 0 Random effects model
			Chronic lung disease	Hospitalization (no CLD) (4 studies)	OR 1.98 (1.04-3.74)	I^2= 61.0 Random effects model
				ICU admission (no CLD) (9 studies)	OR 1.06 (0.89 – 1.25)	I^2= 0.0 Random effects model
				Mortality (no CLD) (18 studies)	OR 3.12 (2.17-4.49)	I^2= 3.95 Random effects model
			Smoking	Hospitalization (no smoking) (8 studies)	OR 1.04 (0.7-1.54)	I^2= 60.5 Random effects model
				ICU admission (no smoking) (9 studies)	OR 1.00 (0.77-1.29)	I^2= 17.1 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
				Mortality (no smoking) (22 studies)	OR 1.36 (1.10-1.67)	I^2= 10.5 Random effects model
			Diabetes	Hospitalization (no diabetes) (8 studies)	OR 3.01 (1.99-4.56)	I^2= 77.1 Random effects model
				ICU admission (no diabetes) (22 studies)	OR 1.58 (1.29-1.93)	I^2= 30.9 Random effects model
				Mortality (no diabetes) (54 studies)	OR 2.14 (1.82-2.52)	I^2= 56.3 Random effects model
			Chronic kidney disease	Hospitalization (no CKD) (7 studies)	OR 5.89 (3.16-11)	I^2= 72 Random effects model
				ICU admission (no CKD) (13 studies)	OR 1.48 (1.08-2.03)	I^2= 26.2 Random effects model
				Mortality (no CKD) (29 studies)	OR 2.36 (1.89-2.94)	I^2= 17.5 Random effects model
			Cancer	Hospitalization (no cancer) (4 studies)	OR 1.64 (0.95-2.84)	I^2= 64 Random effects model
				ICU admission (no cancer) (14 studies)	OR 1.29 (1.02-1.64)	I^2= 9.2 Random effects model
				Mortality (no cancer) (28 studies)	OR 2.08 (1.55-2.77)	I^2= 40.6 Random effects model
			Liver disease	ICU admission (no LD) (10 studies)	OR 1.32 (0.84-2.08)	I^2= 0.0 Random effects model
				Mortality (no LD) (15 studies)	OR 1.32 (0.85-2.04)	I^2= 0.6 Random effects model
			Digestive system disease	Mortality (no GI disease) (5 studies)	OR 1.67 (0.81-3.45)	I^2= 0.0 Random effects model
			Immunosuppressive therapy	ICU admission (no immunosuppression) (5 studies)	OR 0.78 (0.34-1.77)	I^2= 7.1 Random effects model
				Mortality (no immunosuppression) (5 studies)	OR 1.33 (0.62-2.86)	I^2= 48.2 Random effects model
			Anti-retroviral treatment	ICU admission (no ART) (11 studies	OR 0.57 (0.21-1.52)	I^2= 68.4 Random effects model
				Mortality (no ART) (11 studies)	OR 0.57 (0.21-1.52)	I^2= 68.4 Random effects model
Kaur, Charkrabarti & Upinder	SR & MA Any study type Search to July 2020 N= 47 articles	Renin–angiotensin–aldosterone system blockers (ACEI/ARBs)	Hospitalization outcome (n= 15295 (7 studies))	Hospitalization (no RAAS)	OR 2.49 (1.40-4.41)	I^2= 96 Random effects model
			ICU admission outcome (n= 16441 (13 studies)	ICU admission (no RAAS)	OR 1.44 (1.14-1.83)	I^2= 35% Fixed effects model
			Mortality outcome (n= 26432 (31 studies))	Mortality (no RAAS)	OR 0.91 (0.65-1.26)	I^2= 89% Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
Kaur et al.	SR & MA Any study type (no case series) Search to August 2020 N= 5	Asthma	Mortality outcome (all) (n= 10028)	Mortality (no asthma)	OR = 0.96 (0.70–1.30)	I^2= 0 Random effects model
Khan et al.	SR & MA Observational studies Search to February 2021 N= 9	Pregnancy	ICU admission outcome (n= 424,587, 5 studies)	ICU admission (non-pregnant)	RR 2.26 (1.68-3.05)	
			Mortality outcome	Mortality (non-pregnant)	RR 1.08 (0.89-1.31)	
Kollias et al.	SR & MA Any study type Search Feb 2020- March 2021 N= 22 articles	Statins	Mortality outcome (n= 72,881, 12 studies)	Mortality (no statin use)	pOR 0.65 (0.55-0.78)	I^2= 61% Multivariate regression
Kumar et al.	SR & MA Any study type Search to June 2020 N= 8 articles	Fractures	Hip fracture (n= 61)	Mortality (non-hip fractures)	OR 9.76 (1.26-75.72)	I^2= 46% Fixed effects model Interacting pathologies
			Lower limb fracture (n= 59)	Mortality (upper limb fracture)	OR 2.94 (0.25- 33.9)	Fixed effects model
La Verde et al.	SR & MA Observational studies Search to February 2021 N=2 articles (neither in Khan et al.)	Pregnancy	Pregnancy * ≥ 1 comorbidity (n= 1281)	Mortality (no comorb)	RR 2.26 (1.77-2.89)	I^2= 76% Random effects model
			Pregnancy * Gestational Diabetes (n= 1281)	Mortality (no diabetes)	RR 5.71 (0.77-42.44)	I^2= 94% Random effects model
			Pregnancy * Obesity (n= 1281)	Mortality (non-obese)	RR 2.48 (1.41-4.26)	I^2=0% Random effects model
			Pregnancy * Asthma (n= 1281)	Mortality (no asthma)	RR 2.05 (0.81 – 5.15)	I^2= 0% Random effects model
			ICU admission outcome (n= 1281)	ICU admission (non-pregnant)	RR 5.09 (2.00-12.98)	I^2= 56% Random effects model
Lee et al.	SR & MA Any study type Search to November 2020 N= 30 articles	ACEI/ARBs	All studies	Mortality (no ACEI/ARBs) Adjusted for confounders	pOR 0.77 (0.62-0.96)	Random effects model
Liang, Zhang, Li, et al.	SR & MA Case control, cross-sectional, cohort study Search to November 2020 N= 40 articles	Coronary heart disease	ICU admission outcome (4 studies)	ICU admission (no CHD)	OR 2.25 [1.34, 3.79]	I^2= 0% Fixed effects model
			Mortality outcome (22 studies)	Mortality (no CHD)	OR 3.75 [2.91, 4.82]	I^2= 73.1% Random effects model
Liang, Luo, Chen et al.	SR & MA Any study type Search to March 2021 N= 14 articles	People living with HIV	Mortality outcome (6 studies)	Mortality (no HIV)	RR 0.96 (0.88-1.06)	I^2= 0% Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
Lim & Pranata	SR & MA Any study type Search to July 2020 N= 4	Hip fracture	Mortality outcome (4 studies)	Mortality (no hip fracture)	RR 7.45 [2.72, 20.43]	I^2= 68.6% Random effects model
Lin et al.	SR & MA Any study type Search to July 2020 N= 27 articles	Chronic kidney disease	All-cause mortality (adjusted) (n= 8465; 4 studies)	Mortality (no CKD)	OR 2.70 (2.06-3.54)	I^2= 25% Fixed effects model
			Hospitalization outcome (adjusted) (n= 5810; 2 studies)	Hospitalization (no CKD)	OR 2.59 (1.92-3.51)	I^2= 0.0 Fixed effects model
Liu, Cao, Du et al.	SR & MA Any study type (no case series) Search to August 2020 N= 159	Asthma	Mortality outcome (n= 5000; 6 studies)	Mortality (no asthma)	RR 0.65; (0.43-0.98)	I^2= 0.0 Random effects model
			Mechanical ventilation outcome (n= 3285; 4 studies)	Mechanical ventilation (no asthma)	RR 1.03 (0.72 -1.46)	I^2= 0.0 Random effects model
Palaidodimos et al.	SR & MA Any study type Search to May 2020 N= 14 articles	Diabetes mellitus	n/a (all studies)	Mortality (no DM)	OR 1.65 (1.35-1.96)	I^2= 77.4 Random effects model
Pardhan et al.	SR & MA Any study type Search to April 2021 N= 37 articles	Asthma and COPD	Asthma	Hospitalization (no asthma) (n= 1087689; 7 studies)	OR 0.87 (0.73-1.04)	I^2= 85.4 Random effects model
				ICU admission (no asthma) (n= 167849; 4 studies)	OR 0.75 (0.54-1.02)	I^2= 87.2 Random effects model
				Mortality (no asthma) (n=876759; 7 studies)	aOR 0.83 (0.12-0.96)	I^2= 61.5 Random effects model
			COPD	Hospitalization (no COPD) (n=588025; 6 studies)	OR 1.39 (1.31-1.48)	I^2= 4.2 Random effects model
				ICU admission (no COPD) (n= 197108; 9 studies)	OR 1.34 (1.14-1.57)	I^2= 66.6 Random effects model
				Mortality (no COPD) (n= 950502; 17 studies)	aOR 1.28 (1.17-1.43)	I^2= 34.5 Random effects model
Patel et al.	SR & MA Observational studies Search to April 2020 N= 11 studies	Cerebrovascular disease	Mortality outcome Age adjusted	Mortality (no CeVD)	OR 1.42 (1.14–1.77)	I^2= 96.1 Random effects model
			ICU outcome Age adjusted	ICU admission (no CeVD)	OR: 1.82 (1.25–2.69)	I^2= 93.4 Random effects model
Patoulias & Doumas	SR & MA Observational studies Search to May 2021 N= 10 articles	DPP-4 Inhibitor	Mortality outcome (n= 6351; 8 studies)	Mortality (other diabetes medications)	RR 1.14 (0.78-1.66)	I^2= 81% Random effects model
Pijls et al.	SR & MA Cohort & Case-control	Any	Male gender	ICU admission (female) (n=1493; 11 studies)	RR 1.38 (1.09 -1.74)	I^2= 32 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
	Search to May 2020 N= 59 articles			Mortality (female) (n= 12792; 14 studies)	RR 1.50 (1.18-1.91)	I^2= 62 Random effects model
			Age ≥ 70	ICU Admission (Age <70) (n= 688; 5 studies)	RR 2.70 (1.59-4.60)	I^2= 69 Random effects model
				Mortality (Age <70) (n= 9222; 5 studies)	RR 3.61 (2.70-4.84)	I^2= 60 Random effects model
Poly et al.	SR & MA Cohort & Comparison design Search to August 2020 N= 17 articles	Obesity	Mortality outcome (16 studies)	Mortality (non-obese)	RR 1.42 (1.24–1.63)	I^2= 67.9 Random effects model
			Obesity * Age ≥ 65 (6 studies)	Mortality (Age < 65)	RR 2.54 (1.62-3.97)	I^2= 89.3 Random effects model
			Obesity * Male gender (6 studies)	Mortality (female)	RR 1.38 (1.25-1.51)	I^2= 9.6 Random effects model
			Obesity * diabetes (11 studies)	Mortality (non-diabetic)	RR 1.19 (1.07-1.32)	I^2= 54.2 Random effects model
			Obesity * hypertension (9 studies)	Mortality (no HTN)	RR 1.07 (0.92-1.25)	I^2= 60.6 Random effects model
			Obesity * CKD (7 studies)	Mortality (no CKD)	RR 1.57 (1.29-1.91)	I^2= 69.2 Random effects model
			Obesity * COPD (5 studies)	Mortality (no COPD)	RR 1.34 (1.18-1.52)	I^2= 16.1 Random effects model
			Obesity * Stroke (2 studies)	Mortality (no stroke	RR 1.80 (0.89-3.64)	I^2= 0 Random effects model
			Obesity * Smoking (6 studies)	Mortality (no smoking)	RR 1.13 (0.91-1.40)	I^2= 46.6 Random effects model
Putri et al.	SR & MA Cohort or Case-cohort design Search to December 2020 N= 12 articles	Parkinson's disease	Mortality outcome (n= 6 studies)	Mortality (no Parkinson's)	OR 2.623 (1.50 – 4.60)	I^2= 91 Random effects model
Rakhmat et al.	SR & MA Any study type Search to March 2021 N= 9 articles	DPP-4 inhibitor	Mortality outcome (n= 9 studies)	Mortality (no DPP-4 inhibitor)	RR 0.76 (0.60-0.97)	I^2= 44.5 Random effects model Significantly affected by metformin and ACEI/ARB medication
Reyes et al.	SR & MA Any study type Search to June 2020 N= 40 articles	Asthma and COPD	COPD No significant interactions	Mortality (no COPD) (n= 18 studies)	OR 2.74 (2.04-3.68)	I^2= 64.1 Random effects model
				ICU Admission (no COPD) (n= 6 studies)	OR 1.39 (0.79-2.44)	I^2= 57.5 Random effects model
			Asthma No significant interactions	Mortality (no asthma) (n= 6 studies)	OR 0.87 (0.66-1.14)	I^2= 10.1 Random effects model
Schlesinger et al.	Living SR & MA Any observational design	Diabetes	Diabetes * Male (n= 10 studies)	Mortality (female)	Summary RR 1.28 (1.02-1.61)	I^2= 28 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
	Search to October 2020 N= 22 articles		Diabetes * Age ≥ 65 (n=6 studies)	Mortality (Age < 65)	SRR 3.49 (1.82-6.69)	I^2= 74 Random effects model
			Diabetes * Age per 5 years (n= 5 studies)	Mortality	SRR 1.43 (1.12-1.83)	I^2= 84 Random effects model
			Diabetes * current smoking (n= 3 studies)	Mortality (non-smoking)	SRR 0.91 (0.79-1.06)	I^2= 0 Random effects model
			Diabetes * overweight (n= 2 studies)	Mortality (normal weight)	SRR 0.72 (0.45-1.16)	I^2= 0 Random effects model
			Diabetes * Obesity (n= 4 studies)	Mortality (non-obese)	SRR 1.06 (0.76-1.49)	I^2= 46 Random effects model
			Diabetes * Hypertension (n= 8 studies)	Mortality (no HTN)	SRR 1.09 (0.77-1.53)	I^2= 41 Random effects model
			Diabetes * CVD (n= 8 studies)	Mortality (no CVD)	SRR 1.56 (1.09-2.24)	I^2= 70 Random effects model
			Diabetes * Cerebrovascular disease (n= 2 studies)	Mortality (no CeVD)	SRR 2.11 (1.36-3.26)	I^2= 0 Random effects model
			Diabetes * CKD (n= 6 studies)	Mortality (no CKD)	SRR 1.93 (1.28-2.90)	I^2= 81 Random effects model
			Diabetes * COPD (n= 5 studies)	Mortality (no COPD)	SRR 1.40 (1.21-1.62)	I^2= 0 Random effects model
			Diabetes * Cancer (n= 3 studies)	Mortality (no cancer)	SRR 1.54 (0.94-2.51)	I^2= 0 Random effects model
			Diabetes * Any comorbidity (n= 2 studies)	Mortality (no comorbidity)	SRR 0.94 (0.45-1.98)	I^2= 42 Random effects model
			Metformin use (n-= 4 studies)	Mortality (No metformin)	SRR 0.50 (0.28-0.90)	I^2= 33 Random effects model
			DPP-4 inhibitor use (n=2 studies)	Mortality (no DPP-4 inhibitor)	SRR 0.90 (0.59-1.36)	I^2= 0 Random effects model
			Sulfonylurea/glinide use (n= 2 studies)	Mortality (no SU/G)	SRR 0.73 (0.49-1.09)	I^2= 0 Random effects model
			Insulin use (n= 5 studies)	Mortality (no insulin)	SRR 1.75 (1.01-3.03)	I^2= 48 Random effects model
			Renin inhibitor use (n= 2 studies)	Mortality (no renin inhibitors)	SRR 1.04 (0.64-1.68)	I^2= 0 Random effects model
			Statins (n= 2 studies)	Mortality (no statins)	SRR 1.38 (0.71-2.66)	I^2= 24 Random effects model
Seidu et al.	SR & MA Any study type Search to May 2020 N= 9 articles	Obesity	BMI ≥ 25 (n= 4 studies)	Mortality (BMI <25)	RR 3.52 (1.32-9.42)	I^2= 66% Random effects model
Sharma et al.	SR & MA Observational studies	Liver disease	Chronic liver disease	Hospitalization (no CLD)	OR 0.96 (0.71, 1.29)	I^2= 0 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
	Search to June 2020 N= 24 articles		Acute liver injury	Hospitalization (no ALI)	OR 2.98 (2.35-3.77)	I^2= 36 Random effects model
Siepmann et al.	SR & MA Any study type Search to April 2020 N= 11 studies	Cerebrovascular disease	ICU outcome (n= 3 studies)	ICU admission (no CeVD)	RR 2.79 (1.83-4.24)	I^2= 35.3 Random effects model
			Mortality outcome (n= 6 studies)	Mortality (no CeVD)	RR 2.18 (1.75-2.70)	I^2=13.2 Random effects model
Singh, Jena, Kumar et al.	SR & MA Any study type Search to July 2020 N= 24 articles	Inflammatory bowel disease	Ulcerative colitis	Hospitalization (Crohn's disease) (n= 2201)	RR 1.55 (1.22-1.97)	I^2=15 Random effects model
				ICU admission (Crohn's disease) (n=2016)	RR 1.42 (0.97-2.07)	I^2=0 Random effects model
				Mortality (Crohn's disease) (n= 2094)	RR 1.94 (1.22-3.10)	I^2=0 Random effects model
Singh, Hussain & Antony	SR & MA Case-control & cohort studies Search to November 2020 N= 13 articles	NAFLD	ICU outcome (n= 2 studies)	ICU admission (no NAFLD)	pOR 1.66 (1.26-2.20) adjusted	I^2=0 Random effects model
			Mortality outcome (n= 2 studies)	Mortality (no NAFLD)	pOR 1.01 (0.65 – 1.58) adjusted	I^2=0 Random effects model
Sitek et al.	SR & MA Any study type Search to October 2020 N= 16 articles	Asthma	Hospitalization outcome (n= 4 studies)	Hospitalization (no asthma)	OR 1.26 (0.29-7.28)	I^2=86.5 Random effects model
			ICU outcome (n= 6 studies)	ICU admission (no asthma)	OR 1.65 (0.65-4.17)	I^2=54.2 Random effects model
			Mortality outcome (n= 12 studies)	Mortality (no asthma)	OR 0.73 (0.38-1.40)	I^2=81.5 Random effects model
Taylor et al.	SR & MA Observational studies Search to February 2021 N= 58 articles	Any	Male sex (n= 55 studies)	Mortality (female)	OR 1.13 (0.98-1.31)	I^2=81.7 Random effects model
			Smoking (n= 21 studies)	Mortality (no smoking)	OR 1.40 (1.03-1.90)	I^2=73.3 Random effects model
			Hypertension (n= 45 studies)	Mortality (no HTN)	OR 1.54 (1.29-1.85)	I^2=81.7 Random effects model
			Diabetes (n= 47 studies)	Mortality (no diabetes)	OR 1.41 (1.22-1.63)	I^2=63.2 Random effects model
			Cardiovascular disease (n= 41 studies)	Mortality (no CVD)	OR 1.91 (1.52-2.38)	I^2=68.2 Random effects model
			Respiratory disease (n= 41 studies)	Mortality (no resp disease)	OR 1.75 (1.33-2.31)	I^2=63.4 Random effects model
			Cerebrovascular disease (n= 12 studies)	Mortality (no CeVD)	OR 1.61 (0.92-2.83)	I^2=57.2 Random effects model
			Renal disease (n= 28 studies)	Mortality (no renal disease)	OR 2.39 (1.68-3.40)	I^2=69.1 Random effects model
			Malignancy (n= 29 studies)	Mortality (no malignancy)	OR 1.81 (1.30-2.52)	I^2=58.3 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
			Liver disease (n= 17 studies)	Mortality (no liver disease)	OR 1.29 (0.85-1.97)	I^2=30.5 Random effects model
Wang, Chen, Chen et al.	SR & MA Any study type Search to June 2020 N= 4 articles	Asthma	Mortality outcome (n= 4 studies)	Mortality (no asthma)	OR 0.96 (0.70-1.30)	I^2=0 Random effects model
Wang, Luo, Zhang et al.	SR & MA Any study type Search to May 2020 N= 42 articles	Kidney Disease	Chronic kidney disease (n= 11 studies)	Mortality (no CKD)	OR 5.11 (3.36-7.77)	I^2=0 Random effects model
			Acute kidney injury (n= 6 studies)	Mortality (no AKI)	OR 30.46 (18.33-50.95)	I^2=42 Random effects model
Wu et al.	SR & MA Any study type Search to April 2021 N= 24 studies	Asthma	Hospitalization outcome (n= 10 studies)	Hospitalization (no asthma)	OR 0.91 (0.76-1.10)	I^2=79.1 Random effects model
			ICU outcome (n= 15 studies)	ICU outcome (no asthma)	OR 1.17 (0.81-1.68)	I^2=91.1 Random effects model
			Mortality outcome (adjusted) (n= 21 studies)	Mortality (no asthma)	OR 0.95 (0.78-1.15)	I^2=63.5 Random effects model
Xiang et al.	SR & MA Cross-sectional studies Search to June 2020 N= 20 studies	Any	Age ≥ 60 years (n= 7 studies)	Mortality (age < 60 years)	OR 4.94 (2.89-8.44)	I^2=86 Random effects model
			Female sex (n= 20 studies)	Mortality (Male)	OR 0.66 (0.59-0.73)	I^2=29.3 Random effects model
			Current Smoking (n= 9 studies)	Mortality (non-smoking)	OR 1.51 (1.23-1.85)	I^2=32.7 Random effects model
			Hypertension (n= 18 studies)	Mortality (no HTN)	OR 2.26 (1.73-2.95)	I^2=77.4 Random effects model
			Cardiovascular disease (n= 20 studies)	Mortality (no CVD)	OR 2.52 (2.21-2.89)	I^2=49.6 Random effects model
			Diabetes (n= 17 studies)	Mortality (no diabetes)	OR 1.63 (1.44-1.84)	I^2=29.1 Random effects model
			Respiratory disease (n= 17 studies)	Mortality (no resp disease)	OR 2.55 (2.14-3.05)	I^2=37.2 Random effects model
			Chronic kidney disease (n= 9 studies)	Mortality (no CKD)	OR 1.82 (1.46-2.28)	I^2=0 Random effects model
			Cancer (n= 10 studies)	Mortality (no cancer)	OR 1.43 (1.12-1.82)	I^2=22.4 Random effects model
Yang, Cai & Zhang (2021a)	SR & MA Any study type Published in October 2020 N= 4 studies	DPP-4 Inhibitors	Mortality outcome	Mortality (no DPP-4i)	OR 0.58 (0.34-0.88)	I^2=51.1 Random effects model
Yang, Cai & Zhang (2021b)	SR & MA Any study type	Insulin treatment in people with diabetes	Mortality outcome (n= 12 studies)	Mortality (no insulin treatrment)	OR 2.10 (1.51-2.93)	I^2=71.5 Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
	Published in Feb 2021 N= 18 articles		Hospital admission outcome (n= 5 studies)	Hospitalization (no insulin treatment)	OR 1.23 (0.65-2.33)	I^2=87.6 Random effects model
			Type 2 DM (n= 2 studies)	Hospitalization (no insulin treatment)	OR 1.31 (1.06-1.61)	I^2=0 Random effects model
			Type 1 DM (n= 2 studies)	Hospitalization (no insulin treatment)	OR 1.23 (0.65-2.33)	I^2=87.6 Random effects model
Yang, Tian, Chen et al.	SR & MA Observational studies Search to July 2020 N= 41	Obesity (BMI≥30) Overweight (BMI≥ 25)	Obesity	Hospitalization (no obesity) (n= 25,403)	OR = 1.54, (1.33–1.78)	I^2=60.9 Random effects model
				ICU admission (no obesity) (n= 4086)	OR 1.48 (1.24-1.77)	I^2=67.5 Random effects model
				Mortality (no obesity) (n= 8259)	OR 1.14 (1.04-1.26)	I^2=74.4 Random effects model
			BMI 25-30	Hospitalization (BMI <25)	OR = 1.30 (1.09–1.57)	I^2=0 Random effects model
				ICU admission (BMI <25)	OR = 1.90 (0.89–4.07)	I^2=0 Random effects model
				Mortality (BMI < 25)	OR = 1.06, (0.79–1.42)	I^2=0 Random effects model
			BMI 30-40	Hospitalization (BMI <25)	OR = 2.09, (1.34–3.26)	I^2=95 Random effects model
				ICU admission (BMI <25)	OR = 1.44, (0.67–3.09)	I^2=0 Random effects model
			BMI 30-35	Mortality (BMI < 25)	OR = 1.01, (0.74–1.39)	I^2=0 Random effects model
			BMI 35-40	Mortality (BMI < 25)	OR = 1.32, (0.88–1.96)	I^2=0 Random effects model
			BMI ≥40	Hospitalization (BMI <25)	OR = 2.76, (1.76–4.32)	I^2=25.8 Random effects model
				ICU admission (BMI <25)	OR = 2.19, (0.51–9.35)	I^2=63.8 Random effects model
				Mortality (BMI < 25)	OR = 1.56, (1.07–2.26)	I^2=0 Random effects model
Zhang, Ma, Han et al.	SR & MA Any study type Search to February 2021 N= 109 articles	Smoking history	Any smoking (current and former)	Mortality (never smoked) (n= 44 studies)	OR 1.58 (1.38-1.81)	I^2=79.5 Random effects model
				ICU admission (never smoked) (n= 14 studies)	OR 1.73 (1.36-2.19)	I^2=55.6 Random effects model
Zhang, Lewis, Moley et al.	SR & MA Any study type Search to May 2020 N= 22 articles	Obesity (BMI ≥30)	Hospitalization outcome (n= 6252; 4 studies)	Hospitalization (non-obese)	OR 1.68 (1.28-2.188)	I^2 not described Random effects model
			ICU outcome (n= 8 studies)	ICU admission (Non-obese)	OR 1.35 (1.14-1.59)	I^2= not described Random effects model

Reference	Study Description	Population of Interest	Subgroup	Outcome (Reference)	Associated Risk	Notes
			Mortality outcome (n= 9 studies)	Mortality (non-obese)	OR 0.96 (0.74-1.25) (not stable in sensitivity analysis)	I^2= not described Random effects model
Zhang, Wu, Xu et al.	SR & MA Cohort studies Search to October 2020 N= 25 articles	Renin-angiotensin-aldosterone system inhibitors (ACEI/ARBs)	General population	ICU admission (no RAAS inhibitors) (n= 7 studies)	OR 1.14 (0.57-1.71)	I^2=89.7 Random effects model
				Mortality (no RAAS inhibitors) (n= 7 studies)	OR 0.98 (0.75-1.22)	I^2=13.6 Random effects model
			Hypertension	ICU admission (no RAAS inhibitors) (n= 7 studies)	OR 0.36 (0.19-0.53)	I^2=88.3 Random effects model
				Mortality (no RAAS inhibitors) (n= 14 studies)	OR 0.51 (0.29 – 0.73)	I^2=73.4 Random effects model
Zippi et al.	SR & MA Cohort & Case-control studies Search to November 2020 N= 5 articles	Proton Pump Inhibitors	Mortality outcome (n= 5 studies)	Mortality (no PPI)	OR 1.77 (0.62 – 5.03)	I^2=89.0 Random effects model

C. Methods

Literature Search

A literature search was conducted by Rachel Zhao from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published in 2021 and included: Ovid Medline, EMBASE, and MedRxiv. The full strategy is included in Appendix D below. Briefly, the search strategy involved combinations of keywords and subject headings including for the following concepts:

- SARS-CoV-2 / COVID-19
- Severe outcomes (hospitalization, ICU admission, ventilation, death)
- Risk factors for severe disease (identified in the first version of this review)

Articles identified by KRS in their search were initially screened for obvious irrelevance and de-duplicated by the librarian. Relevant, unique articles were then screened by title and abstract against the inclusion/exclusion criteria listed in Table 44 below. 303 articles were identified by KRS with references and abstracts provided for further review. 170 articles were excluded based on information in the title and abstract, and a further 64 articles were excluded following full-text screening. A total of 234 articles were excluded from the review in accordance with the inclusion/exclusion criteria stated below, leaving 69 articles for inclusion in the narrative synthesis.

Table 44. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- Any population - SR includes epidemiological studies describing association between age, medical condition, biological determinants, lifestyle factors and severe outcomes of COVID - Relative risk or odds of death - Relative risk or odds of mechanical ventilation or ICU admission (ICU admission preferred) - Relative risk or odds of hospital admission (non-icu) - 2020-2021 - Any jurisdiction - Peer-reviewed - Preprint	- Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - No measure of association calculated - Hypotheses / hypothesis generating study regarding comorbidity and COVID - Therapeutic implications of comorbidity and COVID - Association between lab values and COVID symptoms and disease severity - Prevalence among specified populations - Co-morbidity related patient management - Single studies (any methodology)

- Systematic review, meta-analyses - Search ends after March 30, 2020	- Case report, case series <20 patients, commentary, narrative review, modelling study, editorial, conference abstract, protocol - No search date

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non-peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 45 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Urwin, Gavinder & Graziadio, 2020; Viswanathan et al, 2012; Wynants et al., 2020; Brouwers et al., 2010).

Table 45. Narrative overview of the literature included in this review.

	Description
Volume	Only systematic reviews that included quantitative meta-analysis were considered for inclusion. 69 articles were included.
Quality	Upon brief inspection, the included meta-analyses appear to be of reasonable quality. All included their search strategies, a PRISMA diagram, a funnel plot analyzing publication bias, and considered heterogeneity in their statistical analysis (even if it was not displayed in the figures). The evidence was inconsistent with respect to confounding and interaction effects. Some authors performed meta-regression to identify confounders, others used pre-adjusted data, and some authors did not address interaction effects at all. The quality of the evidence base underpinning the meta-analyses was not appraised in this review; however, past experience suggests that primary studies on COVID-19 epidemiology often are of moderate quality at best. Observational studies of patient characteristics are not subject to the selection bias and under-planning that plague many experimental studies on COVID-19. The commentary on quality in the

	previous SAG reviews on this topic likely still stand: over-representation of the COVID-19 experience from the eastern United States, Italy, and China may have overlapping datasets that could bias the measures of association away from the null.
Applicability	All of the evidence included in the meta-analyses was collected throughout 2020 and the early part of 2021, making it very thorough for wild-type SARS-CoV-2. However, it is still too early for systematic reviews of Alpha and Delta variants or of patients with severe post-vaccination breakthrough infections to be available. This limits the applicability of this review; however, it is unlikely that risk factors for variant SARS-CoV-2 are different from wild-type SARS-Cov-2 in unvaccinated populations. Systematic reviews are conducted without jurisdictional boundaries, making the results of this review applicable to Alberta.
Consistency	The reported meta-analyses and findings were highly consistent. This may be due to overlap between included studies for some conditions; however, the primary evidence identified in the previous iteration of this review was also very consistent. This suggests that the results of this synthesis are reliable.

D. Search Strategy

Ovid MEDLINE(R) ALL 1946 to October 25, 2021

#	Searches	Results
1	exp Coronavirus/ or Coronavirus Infections/ or COVID-19/ or (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or severe acute respiratory syndrome coronaviru* or severe acute respiratory syndrome cov 2 or 2019 ncov or 2019ncov).kw,tw.	206114
2	exp Mortality/	408280
3	exp Respiration, Artificial/	83206
4	exp Critical Care/	62222
5	intensive care units/ or exp intensive care units, pediatric/ or intensive care units, neonatal/ or respiratory care units/	87138
6	exp Hospitalization/	266888
7	(motalit* or death rate* or cause of death or survival rate* or mechanical ventilat* or artificial respirat* or critical care or intensive care or intensive care unit* or ICU* or PICU* or NICU* or respiratory care unit* or hospitaliz* or hospitalis* or patient admission* or hospital admission*).ti,kw.	162864
8	(motalit* or death rate* or cause of death or survival rate* or mechanical ventilat* or artificial respirat* or critical care or intensive care or intensive care unit* or ICU* or PICU* or NICU* or respiratory care unit* or hospitaliz* or hospitalis* or patient admission* or hospital admission*).ab. /freq=2	276278
9	or/2-8	970760
10	exp Age Factors/	521956
11	exp Pulmonary Disease, Chronic Obstructive/	60647
12	exp Asthma/	134098
13	exp Renal Insufficiency, Chronic/	123214
14	exp Diabetes Mellitus/	457683
15	exp Obesity/	233101
16	exp Hypertension/	299836
17	exp Blood Pressure/	299499
18	exp Gastrointestinal Diseases/	1006472
19	exp Nervous System Diseases/	2657855
20	exp Liver Diseases/	583791

21	exp Thyroid Diseases/	153740
22	exp Pregnancy/	939106
23	Sex/	7694
24	(age factor* or chronic obstructive pulmonary disease* or chronic pulmonary disease* or diabet* or asthma* or chronic renal insufficienc* or chronic kidney disease* or chronic renal disease* or chronic kidney insufficienc* or chronic kidney failure* or chronic renal failure* or end stage kidney disease* or end stage renal disease* or obesity or obese or hypertension or high blodd pressure* or gastrointestinal disease* or gastrointestinal disorder* or ((nervous or neurologic*) adj1 (disease* or disorder*)) or liver disease* or liver dysfunction* or thyroid disease* or pregnan* or sex).ti,kw.	1320852
25	(age factor* or chronic obstructive pulmonary disease* or chronic pulmonary disease* or diabet* or asthma* or chronic renal insufficienc* or chronic kidney disease* or chronic renal disease* or chronic kidney insufficienc* or chronic kidney failure* or chronic renal failure* or end stage kidney disease* or end stage renal disease* or obesity or obese or hypertension or high blodd pressure* or gastrointestinal disease* or gastrointestinal disorder* or ((nervous or neurologic*) adj1 (disease* or disorder*)) or liver disease* or liver dysfunction* or thyroid disease* or pregnan* or sex).ab. /freq=2	1205688
26	exp Heart Diseases/	1189385
27	(heart disease* or heart disorder*).ti,kw.	71813
28	(heart disease* or heart disorder*).ab. /freq=2	32063
29	or/26-28	1203864
30	chronic.ti,kw.	456767
31	chronic.ab. /freq=2	329215
32	30 or 31	639503
33	29 and 32	43948
34	or/10-25,33	7138414
35	1 and 9 and 34	5301
36	severe outcome*.ti.	151
37	1 and 36	48
38	35 or 37	5336
39	limit 38 to (yr="2021" and english)	2946
40	remove duplicates from 39	2919
41	limit 40 to (meta analysis or "systematic review")	142

E.

F. **Embase** 1996 to 2021 Week 42

#	Searches	Results
1	COVID-19/ or SARS-CoV-2/ or coronavirinae/ or betacoronavirus/ or Coronavirus infection/ or (covid or coronavirus* or corona viru* or coronavirinae* or covid2019 or covid19 or covid-19 or nCoV* or n-CoV* or novel CoV* or 2019-nCoV* or 2019nCoV or 19nCov or hCoV* or h-Cov* or 2019-hCoV* or 2019hCoV* or 19 hCoV* or SARS-CoV-2 or SARSCoV2 or SARSCov-2 or SARS-CoV-19 or SARSCoV19 or SARSCoV-19 or SARS-Cov-2019 or SARSCoV2019 or SARSCoV-2019 or "severe acute respiratory syndrome CoV 2" or "severe acute respiratory syndrome coronavirus 2").kw,tw.	203289
2	exp mortality/	1093381
3	exp mechanical ventilator/	4794
4	exp artificial ventilation/	178544
5	exp intensive care/	654318
6	intensive care unit/ or medical intensive care unit/ or neonatal intensive care unit/ or pediatric intensive care unit/	199620
7	exp hospitalization/	408973
8	(motalit* or death rate* or cause of death or survival rate* or mechanical ventilat* or artificial respirat* or critical care or intensive care or intensive care unit* or ICU* or PICU* or NICU* or respiratory care unit* or hospitaliz* or hospitalis* or patient admission* or hospital admission*).ti,kw.	211955
9	(motalit* or death rate* or cause of death or survival rate* or mechanical ventilat* or artificial respirat* or critical care or intensive care or intensive care unit* or ICU* or PICU* or NICU* or respiratory care unit* or hospitaliz* or hospitalis* or patient admission* or hospital admission*).ab. /freq=2	428103
10	or/2-9	2150452
11	exp age/	756700
12	exp chronic obstructive lung disease/	135545
13	exp asthma/	227969
14	exp chronic kidney failure/	96748
15	exp diabetes mellitus/	947681
16	exp obesity/	539405
17	exp hypertension/	681730
18	exp blood pressure/	504347
19	exp gastrointestinal disease/	84758
20	exp neurologic disease/	3129733

21	exp liver disease/	897473
22	exp thyroid disease/	192902
23	exp pregnancy/	475182
24	exp sex/	322888
25	(age factor* or chronic obstructive pulmonary disease* or chronic pulmonary disease* or diabet* or asthma* or chronic renal insufficienc* or chronic kidney disease* or chronic renal disease* or chronic kidney insufficienc* or chronic kidney failure* or chronic renal failure* or end stage kidney disease* or end stage renal disease* or obesity or obese or hypertension or high blodd pressure* or gastrointestinal disease* or gastrointestinal disorder* or ((nervous or neurologic*) adj1 (disease* or disorder*)) or liver disease* or liver dysfunction* or thyroid disease* or pregnan* or sex).ti,kw.	1402581
26	(age factor* or chronic obstructive pulmonary disease* or chronic pulmonary disease* or diabet* or asthma* or chronic renal insufficienc* or chronic kidney disease* or chronic renal disease* or chronic kidney insufficienc* or chronic kidney failure* or chronic renal failure* or end stage kidney disease* or end stage renal disease* or obesity or obese or hypertension or high blodd pressure* or gastrointestinal disease* or gastrointestinal disorder* or ((nervous or neurologic*) adj1 (disease* or disorder*)) or liver disease* or liver dysfunction* or thyroid disease* or pregnan* or sex).ab. /freq=2	1620262
27	exp heart disease/	1655995
28	(heart disease* or heart disorder*).ti,kw.	58805
29	(heart disease* or heart disorder*).ab. /freq=2	39793
30	or/27-29	1664362
31	chronic.ti,kw.	444957
32	chronic.ab. /freq=2	428601
33	31 or 32	693514
34	30 and 33	77690
35	or/11-26,34	7348633
36	1 and 10 and 35	19337
37	severe outcome*.ti.	202
38	1 and 37	52
39	36 or 38	19365
40	limit 39 to (english language and yr="2021 -Current")	10605
41	limit 40 to exclude medline journals	2235
42	limit 41 to (meta analysis or "systematic review")	131

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