Prognostic factors of COVID-19: an umbrella review endorsed by the International Society for Pharmacoepidemiology

Authors: Grammati Sarri,[1] Wei Liu,[2] Luke Zabotka,[3] Andreas Freitag,[1] Ravinder Claire,[4] Grace Wangge,[5] Jamie Elvidge,[4] Dalia Dawoud,[4,6] Dimitri Bennett[7,8], Xuerong Wen,[9] Xiaojuan Li,[10] Christopher T. Rentsch,[11,12] Md Jamal Uddin,[13,14] M Sanni Ali,[15,16] Mugdha Gokhale,[17] Anouk Déruaz-Luyet[18], Daniela C. Moga[19], Jeff Jianfei Guo[20], Andrew R. Zullo[21], Elisabetta Patorno[3], Kueiyu Joshua Lin[3]

Affiliations

[1] Cytel, London, UK

[2] Office of Surveillance and Epidemiology, CDER, US Food and Drug Administration

[3] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

[4] National Institute for Health and Care Excellence, London, UK

[5] Monash University, Indonesia

[6] Cairo University, Cairo, Egypt

[7] Takeda Development Center Americas, Inc., Cambridge, MA, US

[8] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, US

[9] College of Pharmacy, University of Rhode Island, Kingston, RI, US

[10] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, US

[11] Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK

[12] Department of Internal Medicine, Yale School of Medicine, New Haven, CT, US

[13] Department of Statistics, Shahjalal University of Science and Technology, Sylhet 3114, Bangladesh

[14] Department of General Educational Development (GED), Daffodil International University, Dhaka, Bangladesh

[15] Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, London, UK

[16] Liverpool School of Tropical Medicine, Liverpool, UK

[17] Pfizer Inc, New York, NY, US

[18] Boehringer Ingelheim International GmbH. Ingelheim-am-Rhein, Germany

[19] Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky, Lexington, KY, US

[20] Division of Pharmacy Practice & Administrative Sciences, College of Pharmacy, University of Cincinnati, Cincinnati, OH, US

[21] Department of Epidemiology, School of Public Health, Brown University, Providence, RI, US

Declarations

GS and AF are employed by Cytel, Inc.

DB is an employee of Takeda.

LZ, MSA report no declarations.

XL receives research support from the NIH (R03AG070661 and K01AG073651).

ARZ receives grant funding paid directly to Brown University by Sanofi for collaborative research on the epidemiology of infections and vaccinations in nursing home residents and infants. ARZ also receives grant funding from the U.S. National Institute on Aging (R01AG077620, R01AG065722).

EP is investigator of a research grant to the Brigham and Women's Hospital from Boehringer-Ingelheim, not related to the topic of this work. EP receives research grants from the Patient Centered Outcomes Research Institute (DB-2020C2-20326) and the Food and Drug Administration (5U01FD007213), not related to the topic of this work.

All other authors declared no competing interests for this work.

Funding

This work was partly funded by ISPE and also received support from the European Health Data and Evidence Network (EHDEN) project. EHDEN received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No. 806968. The JU receives support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Abstract

During the COVID-19 pandemic, the urgency for updated evidence to inform public health and clinical care placed systematic literature reviews (SLR) at the cornerstone of research.

We aimed to summarize evidence on prognostic factors for COVID-19 outcomes through published SLRs and to critically assess quality elements in the findings' interpretation.

An umbrella review was conducted via electronic databases from January 2020 to April 2022. All SLRs (and meta-analyses) in English were considered. Data screening and extraction were conducted by two independent reviewers. AMSTAR 2 tool was used to assess SLR quality. The study was registered with PROSPERO (CRD4202232576).

Out of 4,564 publications, 171 SLRs were included of which 3 were umbrella reviews. Our primary analysis included 35 SLRs published in 2022 which incorporated studies since the beginning of the pandemic. Consistent findings showed that, for adults, older age, obesity, heart disease, diabetes, and cancer were more strongly predictive of risk of hospitalization, intensive care unit admission, and mortality due to COVID-19. Male sex was associated with higher risk of short-term adverse outcomes, but female sex was associated with higher risk of long COVID. For children, socioeconomic determinants that may unravel COVID-19 disparities were rarely reported.

This review highlights key prognostic factors of COVID-19, which can help clinicians and health officers identify high-risk groups for optimal care. Findings can also help optimize confounding adjustment and patient phenotyping in comparative effectiveness research. A living SLR approach may facilitate dissemination of new findings. This paper is endorsed by the International Society for Pharmacoepidemiology.

Introduction

The new coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the emergence of novel and evolving variants has placed unprecedented pressure on patients' livelihoods, healthcare systems, community organizations, and financial systems worldwide due to the fast spreading nature of the disease and its massive clinical, societal, and economic burden (1,2). Since COVID-19 was declared a worldwide pandemic by the World Health Organization (WHO) in February 2020, a plethora of studies has been conducted to identify potential predictors of adverse clinical outcomes supporting policymakers and clinicians in making urgent, evidence-informed decisions for disease management at both patient and healthcare system levels (3). Evidence synthesis through systematic literature reviews (SLR), with or without meta-analyses, is the cornerstone of evidence-based decision-making and central to optimizing healthcare for patients (4). This has been especially important during the pandemic where the need for reliable and dynamic data placed SLRs at the forefront of COVID-19 research (5).

Prognostic tools for the prediction of COVID-19 severity in patients have been in development since early 2020. However, concerns were raised about the validity of some of these prediction tools because they were developed based on observational data when healthcare systems were overwhelmed by the patient surge and have variable and questionable data and methodological quality. Lack of reporting standards also makes it difficult to compare or synthesize results across studies. A living systematic review concluded that most published prediction models of COVID-19 severity were poorly reported and at high risk of bias, resulting in predictive performances that are probably overly optimistic. Furthermore, the few models with low risk of bias were not validated in different settings and populations to demonstrate generalizability and transportability of their findings (6).

Several SLRs on COVID-19 risk factors or prognostic tools have been published. However, it has been challenging to interpret and compare these findings in the rapidly evolving pandemic with changing SARS-CoV-2 viral virulence, vaccine availability, treatment options, and healthcare systems preparedness. The rapid generation of new data created a complex, and often confusing, picture of which factors could significantly and independently affect disease outcomes.

Recognizing individual prognostic factors that are significantly associated with COVID-19 disease severity and progression is essential to produce robust clinical practice guidelines to guide clinical decision-making and provide tailored prevention and management strategies. This can be done through two main channels: at the public health level, by identifying patient subgroups who are most at risk for developing complications or adverse COVID-19-related outcomes and targeting appropriate interventions such as vaccination programs, optimizing monitoring strategies, and

providing earlier access to hospital care (7); and at the research level, by informing the design of clinical trials or real-world evidence (RWE) studies.

In comparative effectiveness research assessing preventive or therapeutic approaches to COVID-19 based on non-randomized studies (NRS), identification of the predictors and risk factors of COVID-19 is critical for optimizing the validity of treatment effect heterogeneity evaluation and confounding (8). Thus, we aimed to conduct an umbrella review (i.e., SLR of SLRs) that systematically provides a comprehensive synthesis, assesses quality, and compares findings from all available SLRs on risk factors for COVID-19 disease severity and progression.

Methodology

We conducted an umbrella review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement 2020 (9) and the study protocol was registered with PROSPERO (CRD4202232576).

Electronic databases (MEDLINE and MEDLINE In-Process, Embase, Evidence-Based Medicine Reviews, health technology assessment, LitCovid (National Center for Biotechnology Information-National Library of Medicine-National Institutes of Health), Cochrane Library, and WHO COVID-19 Research Database) were searched for relevant studies published from January 31, 2020 through April 30, 2022 (see Supplementary File 1 for search terms and strategies).

SLRs (with or without meta-analysis results) were eligible for inclusion if they met all the following criteria: 1) assessed the role of one or multiple factors (e.g., sociodemographic, comorbidities, etc.) as predictors or risk factors of COVID-19 disease severity or progression; 2) were published as full-text, freely accessible papers (open access); and 3) were available in English. Narrative reviews and commentaries were not considered, and there was no restriction by geography or age. Predictors or risk factors in this study were defined as “any measure that is associated with a subsequent clinical outcome among people with COVID-19” (6). We considered all types of predictors or risk factors including demographic and anthropometric individual characteristics, medical history, and comorbid diseases. As measures of COVID-19 disease severity, we captured all key short-term outcomes during the first episode of infection (composite severity outcomes, hospitalization, intensive care unit [ICU] admission, mortality) and long-term (i.e., “long COVID” defined as ongoing symptoms in individuals with a history of SARS-CoV-2 infection, lasting for at least two months following initial recovery that cannot be explained by an alternative diagnosis) COVID-19-related outcomes (10).

Prognostic or prediction models of COVID-19 outcomes were excluded since these models are mainly used to guide individualized patient care decisions. This was not aligned with the objective of this review which aimed to support decisions regarding the selection of key predictors and risk factors to inform confounding adjustment and effect heterogeneity in analyses of real-world data in the setting of comparative effectiveness research. In addition, SLRs investigating the role of clinical factors arising during the acute phase of the infection (e.g., symptoms), or use of specific treatments, SLRs focusing on pre-defined diseased populations with COVID-19 (with no presence of a control group) or SLRs with no quantitative data of the included studies were excluded. Supplementary File 1 presents the protocol details.

Searches, screening, and article selection were done independently by two reviewers at both abstract and full-text levels using the COVIDENCE platform. Any disagreements were resolved through a discussion with a third senior reviewer.

Data extraction from individual SLRs was conducted in a pre-designed template focusing on key descriptors of SLRs (e.g., data sources, inclusion criteria, reporting details regarding exposure(s) and outcome(s), type of statistical analyses, quality assessment of included studies), and summary results along with measures of uncertainty and heterogeneity, if meta-analysis was performed. A (risk/predictor) factor was deemed "significant" if the included SLR(s) reported a statistically significant measure of association (e.g., odds ratio, risk ratio, or rate difference based on pooled aggregated data or individual patient-level data, or qualitatively based on observations across studies included in the individual SLR). All data extracted were independently validated by a second reviewer.

Trends across the SLRs were identified by qualitative synthesis of the results. The methodological quality of individual SLRs was assessed using the Assessing the Methodological Quality of Systematic Reviews 2 score (11) with additional, COVID-19-related points for consideration as outlined in a recent International Society for Pharmacoepidemiology (ISPE)-endorsed guidance document (8).

Results

Across all searched databases, 4,564 publications were retrieved. Abstract deduplication resulted in exclusion of 59 duplicate studies. After abstract screening, 171 SLRs investigating the role of single or multiple factors in COVID-19 progression were considered for full-text screening. Among the included studies, two were umbrella reviews (12,13) and three living reviews (14–16), all published in 2021. (Figure 1).

Overall, we found 40, 96, and 35 eligible SLRs published in 2020, 2021, and 2022 (until April), respectively. Due to the high volume of retrieved evidence and the anticipated overlap across SLRs with regard to the studies included, we decided to focus on the most recent evidence from the 35 SLRs published in early 2022 (6,17–45) as we expect that SLRs published in 2022 include most of the evidence considered in previous SLRs when assessing the same predictor(s). In addition, we extracted key descriptive information for the included SLRs (fitting our protocol inclusion criteria) published in 2021 (reference citation, type of risk factors/predictors in each SLRs). However, to ensure that no critical information on potentially relevant predictor factors was missed, we also cross-checked if any predictor was only considered in SLRs published in previous years and presented these SLRs separately (Table S1).

Characteristics of SLRs Published between January 2022 and April 2022

Table S2 presents an overview of individual SLR characteristics. Thirty-five SLRs published in 2022 were fully extracted and assessed, five of which focused on primary studies in children and young people (46–50). All SLRs followed a clear search strategy with well-defined inclusion and exclusion criteria. Fourteen SLRs (40%) had their protocols pre-registered on the PROSPERO platform; however, only two of them mentioned that this database had also been searched prior to conducting this work to ensure that no prior or ongoing reviews existed on the same subject (15). Furthermore, only three SLRs used consecutive patient recruitment (21,31) or sample size (20) as criteria when selecting individual studies.

In terms of methods used across the SLRs, dual screening by independent reviewers was employed by most reviews (>90%). However, less than half of SLRs performed dual data extraction or a clear extraction validation. Almost all reviews searched more than one literature database with clear inclusion and exclusion search criteria. However, one-third of the included SLRs used a literature search cut-off point in 2020 and thus omitting more recent COVID-19 data.

Most included studies in the SLRs were conducted using observational data. Geographical location (country) and patients' age were the most reported baseline information from the included studies across the included SLRs whereas ethnicity was the most underreported demographic factor (17%). Similarly, COVID-19 diagnostic criteria were either pre-defined as inclusion criteria or presented by the individual studies in only two-thirds of the included SLRs (Table S2).

Of the 35 included SLRs, 22 (63%) explored single risk factors for COVID-19 outcomes with vitamin D deficiency as the most frequently presented topic. Among the SLRs focusing on multiple pre-existing health conditions, cardiovascular disease and obesity were most frequently considered. For children, obesity and multiple comorbidities were the most researched risk factors (Figure 2).

The quality of primary studies was assessed in 86% (30 of 35) of the included SLRs, 11 of which used the Newcastle-Ottawa scale (24,27,34,41,42,44–46,48,51,52), five SLRs used the Quality in Prognostic Studies tool (18,20,21,31,39), and two SLRs used Strengthening the Reporting of Observational studies in Epidemiology (37,47), Risk Of Bias In Non-randomised Studies - of Interventions (43,53), and Grading of Recommendations Assessment, Development and Evaluation (36,38), respectively.

Table S3 presents the SLRs which included meta-analyzed (pooled effects) results and additional information. Study-level data were meta-analyzed in the majority of included SLRs (28 of 35 [80%]) even though high heterogeneity (I2>70%) was observed in >90% of pooled effect estimates. Meta-regression was not commonly presented (seven out of 28 meta-analyses (24,26,33,36–38,41)) with age and sex as the most frequently used adjusted factors. Furthermore, only one SLR, including hospitalized children and young people, attempted to identify individual patient data from the included studies and conducted a multi-level meta-analysis adjusting for age and sex (46).

Evidence Map of Predictors/Risk Factors for COVID-19 Outcomes from Included SLRs

Table 1 presents a color-coded evidence map of the most reported predictors/risk factors for the key outcomes (disease severity, hospitalization, ICU admission, mortality, and post COVID-19). These considerations captured in the quality assessment of individual SLRs are fully presented in Table S4.

Among the demographic characteristics, information regarding their association to adverse COVID-19 outcomes was mainly restricted to age and sex. Age was strongly associated with mortality, ICU admission and long COVID risk, with older adults and younger children being at higher risk for experiencing adverse outcomes. For adults, sex was reversed between short-term outcomes (e.g., mortality, hospitalization, and ICU admission) and long COVID. However, sex did not seem to influence COVID-19 mortality for children. In addition, one SLR focused on the role of smoking showing a strong predictive negative effect for mortality and disease severity among COVID-19 patients (19).

When focusing on evidence gaps related to sociodemographic information, most of the included SLRs in 2022 did not consider the impact of socioeconomic status and ethnicity on disease progression, with only one SLR reporting ethnicity's effect for long COVID and another one stating that results for the impact of socioeconomic factors were inconclusive due to wide variability of reported data across the primary studies (46). We, therefore, searched if any SLRs published in 2021 examined the associations between ethnicity or socioeconomic disadvantage and COVID-19 disease outcomes. Results of these three SLRs are reported in Table 2 which consistently showed the unequal disease burden experienced by ethnic minority groups compared with their White counterparts (54–56). The findings about racial disparities varied substantially by geographical regions and they were associated with other factors such as socioeconomic status, education levels, and neighborhood conditions.

Among the pre-existing comorbidities, there was a trend for obesity, cardiovascular disease, hypertension, chronic pulmonary disease and cancer to be significantly associated with mortality in adults and children after COVID-19 infection. In contrast, the SLRs reported that asthma and respiratory diseases did not seem to increase children's mortality risk after COVID-19 (46,50). Vitamin D deficiency, which was the most studied topic in the included SLRs did not show a consistently significant association with COVID-19 mortality. Although some meta-analyses showed that vitamin D deficiency was linked to the severity from COVID-19 infection (24,35,44), mainly due to the cytokine-storm-mediated effects and the link to other diseases already correlated to severe COVID-19, results did not remain statistically significant when excluding studies with a high risk of bias and unadjusted results (24). Limited evidence was retrieved for the outcomes of hospitalization and ICU admission from the SLRs that focused on adult populations. The two SLRs focused on predictors for long COVID identified age and sex as strong predictors (31,36).

Quality assessment of the included studies

The included SLRs used a wide range of inclusion criteria that may reflect the design heterogeneity commonly reported in prognostic studies. We considered unique quality issues seen in electronic health records studies but also data operational challenges specific to COVID-19 as recommended by a recent ISPE-endorsed publication (8). We found more consistent evidence for some predictors/risk factors compared with others, and this was noted in the findings when possible. There may have been differences in the robustness of results across SLRs (for example, some of them only included observational studies with adjusted results for key confounders or population-based studies (40)), which is reflected in both the quality assessments and through their interpretation such as

supplementary sensitivity analyses. Yet the consistency in the direction of findings across SLRs may reinforce the validity of conclusions in our umbrella review. Some common methodological pitfalls across the included SLRs are outlined below in Figure 3.

Discussion

Continuous assessment and synthesis of the rapidly emerging evidence in COVID-19 is important to better shape our understanding as the body of evidence grows and the profile of the virus changes. Our umbrella review focused on summarizing the evidence on predictors and risk factors for adverse outcomes of COVID-19 from 35 most recently published SLRs in 2022 that incorporate literature across different stages of the rapidly evolving pandemic, including the eras before and after the availability of vaccines and anti-viral treatments and periods across several key COVID-19 variants of concern (Delta and Omicron) (57). We encourage readers to consider the limitations of the primary studies and the related statistical analyses of pooled effect sizes while considering the evidence for these factors. Our umbrella review provides a comprehensive summary and critical appraisal of the literature for the risk factors that are consistently predictive across different SLRs and highlights the ones with inconsistent results at different settings.

In any study that attempts to summarize COVID-19 literature, careful consideration of the context is critical. Key factors that need to be considered include different phases of the pandemic, changes in COVID-19 care guidelines, local healthcare system resources (availability of treatments and vaccines), and public health programs (58). One SLR included in our review conducted a subgroup analysis by continent and found significant differences in COVID-19 outcomes between America, Europe, and Asia (42).

Consistent and critical findings from our umbrella review showed that age, male sex, and underlying comorbidities such as heart disease, diabetes, and cancer had the strongest predictive effect on mortality, hospitalization, and ICU admission due to COVID-19. Another important finding of this study is that obesity either independently or in concert with other comorbidities can increase the risk of adverse outcomes of COVID-19. The role of sex varies by outcomes and populations: for adults, we found that male sex was associated with higher risk of short-term (e.g., mortality, hospitalization, and ICU admission), but female sex was associated with higher risk of long COVID. In contrast, sex did not seem to influence COVID-19 mortality for children. The sparse evidence from two SLRs on long COVID inevitably make these results more exploratory than definitive. Furthermore, it is widely noted that heterogeneity in the definitions and the outcomes associated with post-COVID condition may have hampered the full understanding of its impact, resulting in the need to conduct rigorous meta-analyses. Recent efforts such as the core outcome set for post-COVID-19 in adults may help standardize research in this area and ensure consistent evaluation of related outcomes in clinical settings for adults (59) and children (60). The proposed mechanisms for the observed associations include potential biological effects of COVID-19 infection on inflammatory pathways, immunity or lung function as well as correlation with the changes in availability of healthcare availability and patients' behavior changes during the pandemic (30). In addition, lower socioeconomic status risk factors (such as low income and a need to return to employment in the early weeks after developing COVID-19 may also be associated with the presence of long-COVID 19 symptoms (61).

We stratified our analyses by adults vs children. While some risk factors for COVID-19 severity overlap for the two populations, including obesity and cardiovascular comorbidities, some risk factors appear to be related only in the pediatric population, such as neurological disorders. Chronic

lung diseases were consistently prognostic in the adult population, whereas its associations with severe COVID-19 complications were unclear in the pediatric population. Some of these differences may be explained due to population differences or due to disease definition differences (for example, heart failure may be more frequently caused by congenital heart disease in children and by ischemic heart disease in adults).

In our umbrella review, within adult and pediatric populations, the findings were considered relatively stable across SLRs. This is interesting considering the wide variety of definitions for risk factors and outcomes used across studies. While a previous umbrella review conducted earlier in the pandemic also noted the significant role of pre-existing factors such as heart failure, diabetes, obesity, and cancer for fatal COVID-19 outcomes (62), it is important for the current review to demonstrate the temporal generalizability of these factors with more contemporary studies. Compared with two previous umbrella reviews conducted in 2021 (12,13), we found different associations between smoking and obesity and mortality and severe COVID-19, which can be explained by our inclusion of a higher number of primary studies published up to and including 2022. Interestingly, one of these umbrella reviews concluded, through assessing the evidence from primary studies of the included SLRs, that although older age is associated with COVID-19 disease severity and mortality, there does not appear to be an age threshold above which the risk of COVID-19 increases sharply (12).

Strengths

Our review has several notable strengths. First, we applied an umbrella review approach to summarize the global evidence on the predictors and risk factors of severe COVID-19 outcomes in patients with pre-existing health conditions. We followed a systematic approach using well-established. evidence-based standards (PROSPERO registration, dual screening and reviewing, pre-designed data extraction template) to ensure unbiased selection of evidence. We identified one umbrella review published in 2021 looking at the role of pre-existing health conditions and severe COVID-19 outcomes with the aim to conduct meta-analysis of results from the primary studies of included SLRs (62). However, this umbrella review only included evidence from the earlier phase of the pandemic (search cut-off up to December 2020) and restricted its inclusion to studies with age-adjusted risk estimates as the main objective was the re-analysis of primary data.

Our umbrella review brings a significant contribution to the COVID-19 literature not only by systematically identifying and summarizing the predictors and risk factors that contribute to short- and long-term outcomes of COVID-19 but also by providing an evidence map of potential confounders to be considered in future comparative effectiveness analyses of NRS. We did not attempt to conduct a meta-analysis due to the high heterogeneity in study settings, design, and approach as shown by the individual SLR findings. Evidence directly drawn from real-world data reflecting complex and frail patients in routine care is increasingly considered valuable for decision-making. However, appropriate efforts need to be made when using RWE studies in decision-making to mitigate concerns around misclassification, confounding, selection, and other types of biases through optimal identification and modelling of risk factors in statistical analyses.

Our umbrella review showed that the majority of included SLRs did not apply meta-regression techniques to account for the effect of common covariates (comorbidities, demographics) or other COVID-19 related factors (period of the pandemic, setting, rate of vaccination) for their meta-analyses. This is despite previous publications having widely communicated their importance for analysis and interpretation of findings in COVID-19 research. In some instances, this decision may have been impacted by the lack of available baseline information from the individual studies which

would be necessary to provide a complete picture of the patient profile. Furthermore, use of generic definitions of comorbidities and lack of fully defined outcomes (for example, timelines for mortality assessment) may account for insufficient information for decision-making. Researchers should follow formal pharmacoepidemiology guidance on conducting and reporting findings from observational studies (ISPE (63), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (64), Good Pharmacoepidemiology Practices (65)). They should apply recommended methodologies to conduct SLRs for prognosis studies before applying data synthesis in COVID-19 studies to incorporate disease-specific methodological considerations and allow trustworthy interpretations of biases in the results. Finally, the publication of multiple SLRs on the same research questions conducted around similar times unavoidably creates serious concerns about the research waste at a time of increased need for research capabilities such as during the pandemic, as well as the ethical responsibility to produce justifiable, methodologically sound research findings (66,67). We encourage authors to search for similar research activities in registered databases (such as PROSPERO) before initiating these activities which may be run in parallel with other researchers. Additionally, journal editors should request this level of information as a standard reporting item from authors before a manuscript presenting SLR findings is considered for review.

Limitations

A few limitations should be noted. Due to the unprecedent volume of evidence published in this area and despite following well-established standards (documented search, protocol registration, dual screening, and data extraction), it is possible that our umbrella review may have missed some relevant SLRs. We did not assess the duplication of individual studies included in SLRs or the level of missing data from individual SLRs as this was beyond the scope of this umbrella review. In addition, the included SLRs did not attempt to connect their findings with biological plausibility and, therefore, we did not address this issue when interpreting their findings. In general, the main limitations of the original studies would propagate into the SLRs selecting these studies, and in turn into our umbrella review including the SLRs. Our detailed data synthesis was restricted by evidence included in the recent SLRs published in 2022 although reviews published in earlier years were checked and main aspects were not missed. It is widely recognized that evidence synthesis from studies published earlier in the pandemic may suffer from high heterogeneity due to wide differences in public health measures and guidelines regarding healthcare system resources and organization (e.g., availability of hospital beds, ICU capability, and differences in testing strategies and prioritizing care for high-risk groups (68,69). We do not have sufficient data to unravel the impact of predisposing factors on COVID-19 outcomes from the impact of local medical guidelines, therapeutic decisions made in clinical practice and hospitals, and the role of individualized health behaviors during the pandemic.

Conclusions

As we are transitioning from a COVID-19 pandemic to an endemic setting and more treatments are becoming available to patients, it is equally important to accurately identify patients at risk of developing severe COVID-19 or long COVID to optimize the care and management of this condition. Risk factor identification is also essential for confounding adjustment and treatment effect heterogeneity evaluation in comparative effectiveness research. We found that underlying comorbidities and male sex have been associated with worse short-term COVID-19 outcomes whereas female sex was identified as a risk factor of long COVID. The evidence on the role of ethnicity was restricted to single reviews which found that some ethnic minority groups may disproportionally experience worse disease progression. Lack of full assessment and exploration of potential flaws and biases within the included studies in the SLRs limit the validity and

generalizability of their findings especially when considering the role of multiple interacting, correlational factors. Health inequalities were largely unraveled through the COVID-19 pandemic, though without a good understanding of the potential interaction or accumulation of some of these factors that may create a health disadvantage for specific groups of patients in a specific country or setting. The urgency to publish during COVID-19 should not be at the expense of scientific rigor that can compromise trust in evidence synthesis. Continuous review and assessment of the rapidly emerging evidence in the form of living SLRs and avoidance of redundant research efforts on the same topic by encouraging publishers to request justification of submitted research for publication, can better shape our understanding of the pandemic and avoid spreading confusing messages that can be detrimental to public health. Robust identification of high-risk groups remains a challenging but pivotal issue for COVID-19 research, especially considering the wider socio-political consequences of the pandemic for the global community and the impact on public health. With increasing attention paid to the applicability of RWE in comparative effectiveness research, this umbrella review also provides a case study for robustly identifying and assessing the role of predictors for other disease areas (beyond COVID-19), especially in areas with a high volume of information.

Study Highlights

o **What is the current knowledge on the topic?**

Recognizing individual prognostic factors significantly associated with COVID-19 severity and progression is essential to guide clinical decision and comparative effectiveness research. The rapid generation of new data and multiple reviews published on the same topic created a complex, and often confusing, picture of which factors could significantly and independently affect disease outcomes.

o **What question did this study address?**

We conducted an umbrella review to systematically provide a comprehensive synthesis of the evidence identified from previously conducted systematic reviews and meta-analyses by critically appraising data quality and comparing consistency on findings across reviews reporting on the same topic while considering the impact of a rapidly evolving COVID-19 pandemic.

o **What does this study add to our knowledge?**

Our umbrella review brings a significant contribution to the COVID-19 literature not only by systematically identifying and summarizing the predictors and risk factors that contribute to short- and long-term outcomes of COVID-19 separately for children and adults, but also by providing an evidence map of potential confounders to be considered in future comparative effectiveness analyses of non-randomized studies. Our results also highlighted limitations in the conduct and reporting of existing reviews that can guide researchers for future research and evidence gaps such assessing the impact of ethnicity and health inequalities. With increasing attention paid to the applicability of RWE in comparative effectiveness research, this umbrella review provides a case study for robustly identifying and assessing the role of predictors for other disease areas (beyond COVID-19), especially in areas with a high volume of information and contradictory results.

o How might this change clinical pharmacology or translational science?

This research highlights key prognostic factors for COVID-19 for both children and adults that can further help clinicians identify high-risk groups for optimal healthcare and enable pharmacoepidemiologists optimize confounding adjustment in comparative effectiveness research.

Acknowledgments

This paper is endorsed by ISPE. The authors would like to thank Colleen Dumont and Amruta Radhakrishnan for their editorial support during this manuscript development.

The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the organizations they represent.

Authors contribution:

GS and KJL designed the research. GS wrote the manuscript. All authors reviewed, revised and critically contributed to the manuscript. All authors reviewed and approved the final manuscript draft.

References

1. The COVID Decade: understanding the long-term societal impacts of COVID-19 [Internet]. The British Academy. [cited 2023 Jan 5]. Available from: https://www.thebritishacademy.ac.uk/publications/covid-decade-understanding-the-long-term-societal-impacts-of-covid-19/

2. Osterrieder A, Cuman G, Pan-Ngum W, Cheah PK, Cheah PK, Peerawaranun P, et al. Economic and social impacts of COVID-19 and public health measures: results from an anonymous online survey in Thailand, Malaysia, the UK, Italy and Slovenia. BMJ Open. 2021 Jul 1;11(7):e046863.

3. Sharma J, Rajput R, Bhatia M, Arora P, Sood V. Clinical Predictors of COVID-19 Severity and Mortality: A Perspective. Front Cell Infect Microbiol. 2021 Oct 25;11:674277.

4. Gough D, Davies P, Jamtvedt G, Langlois E, Littell J, Lotfi T, et al. Evidence Synthesis International (ESI): Position Statement. Syst Rev. 2020 Jul 10;9(1):155.

5. Elliott J, Lawrence R, Minx JC, Oladapo OT, Ravaud P, Tendal Jeppesen B, et al. Decision makers need constantly updated evidence synthesis. Nature. 2021 Dec;600(7889):383–5.

6. Wynants L, Calster BV, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ. 2020 Apr 7;369:m1328.

7. Living guidance for clinical management of COVID-19 [Internet]. [cited 2023 Jan 6]. Available from: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-clinical-2021-2

8. Sarri G, Bennett D, Debray T, Deruaz-Luyet A, Soriano Gabarró M, Largent JA, et al. ISPE-Endorsed Guidance in Using Electronic Health Records for Comparative Effectiveness Research in COVID-19: Opportunities and Trade-Offs. Clin Pharmacol Ther. 2022 Nov;112(5):990–9.

9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

10. Post COVID-19 condition (Long COVID) [Internet]. [cited 2023 Jan 6]. Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition

11. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

12. Romero Starke K, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, Seidler A. The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis. BMJ Glob Health. 2021 Dec;6(12):e006434.

13. Harrison SL, Buckley BJR, Rivera-Caravaca JM, Zhang J, Lip GYH. Cardiovascular risk factors, cardiovascular disease, and COVID-19: an umbrella review of systematic reviews. Eur Heart J - Qual Care Clin Outcomes. 2021 Oct 1;7(4):330–9.

14. Asiimwe IG, Pushpakom S, Turner RM, Kolamunnage-Dona R, Jorgensen AL, Pirmohamed M. Cardiovascular drugs and COVID-19 clinical outcomes: A living systematic review and meta-analysis. Br J Clin Pharmacol. 2021 Dec;87(12):4534–45.

15. Dumitrascu F, Branje KE, Hladkowicz ES, Lalu M, McIsaac DI. Association of frailty with outcomes in individuals with COVID-19: A living review and meta-analysis. J Am Geriatr Soc. 2021 Sep;69(9):2419–29.

16. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). Addict Abingdon Engl. 2021 Jun;116(6):1319–68.

17. Akbari A, Fathabadi A, Razmi M, Zarifian A, Amiri M, Ghodsi A, et al. Characteristics, risk factors, and outcomes associated with readmission in COVID-19 patients: A systematic review and meta-analysis. Am J Emerg Med. 2022 Feb;52:166–73.

18. Alzoughool F, Abumweis S, Alanagreh L, Atoum M. Associations of pre-existing cardiovascular morbidity with severity and the fatality rate in COVID-19 patients: a systematic review and meta-analysis. Osong Public Health Res Perspect. 2022 Feb;13(1):37–50.

19. Baker J, Krishnan N, Abroms LC, Berg CJ. The Impact of Tobacco Use on COVID-19 Outcomes: A Systematic Review. J Smok Cessat. 2022;2022:5474397.

20. Bellou V, Tzoulaki I, van Smeden M, Moons KGM, Evangelou E, Belbasis L. Prognostic factors for adverse outcomes in patients with COVID-19: a field-wide systematic review and meta-analysis. Eur Respir J. 2022 Feb;59(2):2002964.

21. Boden I, Bernabeu MO, Dhillon B, Dorward DA, MacCormick I, Megaw R, et al. Pre-existing diabetic retinopathy as a prognostic factor for COVID-19 outcomes amongst people with diabetes: A systematic review. Diabetes Res Clin Pract. 2022 May;187:109869.

22. Çınar F, Ekinci G. Investigation of the effect of comorbidity on mortality in patients with covid-19: A systematic review and meta-analysis. Biointerface Res Appl Chem. 2022;5579–90.

23. Darvishzadeh A, Hasani H, Behrouzinezhad R, Bahmani A, Delavar M. Evaluation of predictors of mortality in patients with COVID-19: a systematic review and meta-analysis. Eurasian Chem Commun. 2022 May 1;4(5):392–401.

24. Dissanayake HA, de Silva NL, Sumanatilleke M, de Silva SDN, Gamage KKK, Dematapitiya C, et al. Prognostic and Therapeutic Role of Vitamin D in COVID-19: Systematic Review and Meta-analysis. J Clin Endocrinol Metab. 2022 Apr 1;107(5):1484–502.

25. El-Qushayri AE, Ghozy S, Reda A, Kamel AMA, Abbas AS, Dmytriw AA. The impact of Parkinson's disease on manifestations and outcomes of Covid-19 patients: A systematic review and meta-analysis. Rev Med Virol. 2022;32(2):e2278.

26. Fabião J, Sassi B, Pedrollo EF, Gerchman F, Kramer CK, Leitão CB, et al. Why do men have worse COVID-19-related outcomes? A systematic review and meta-analysis with sex adjusted for age. Braz J Med Biol Res Rev Bras Pesqui Medicas E Biol. 2022;55:e11711.

27. Halim C, Mirza AF, Sari MI. The Association between TNF-α, IL-6, and Vitamin D Levels and COVID-19 Severity and Mortality: A Systematic Review and Meta-Analysis. Pathogens. 2022 Feb 1;11(2):195.

28. Impact of cancer diagnoses on the outcomes of patients with COVID-19: a systematic review and meta-analysis | BMJ Open [Internet]. [cited 2023 May 22]. Available from: https://bmjopen.bmj.com/content/12/2/e044661

29. Hu Y, Kung J, Cave A, Banh HL. Effects of Vitamin D Serum Level on Morbidity and Mortality in Patients with COVID-19: A Systematic Review and Meta-Analysis. J Pharm Pharm Sci Publ Can Soc Pharm Sci Soc Can Sci Pharm. 2022;25:84–92.

30. Banerjee A, Chen S, Pasea L, Lai AG, Katsoulis M, Denaxas S, et al. Excess deaths in people with cardiovascular diseases during the COVID-19 pandemic. Eur J Prev Cardiol. 2021 Nov 1;28(14):1599–609.

31. Maglietta G, Diodati F, Puntoni M, Lazzarelli S, Marcomini B, Patrizi L, et al. Prognostic Factors for Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis. J Clin Med. 2022 Mar 11;11(6):1541.

32. Jordan T, Siuka D, Rotovnik NK, Pfeifer M. COVID-19 and Vitamin D- a Systematic Review. Zdr Varst. 2022 Jun;61(2):124–32.

33. Li S, Ren J, Hou H, Han X, Xu J, Duan G, et al. The association between stroke and COVID-19-related mortality: a systematic review and meta-analysis based on adjusted effect estimates. Neurol Sci. 2022;43(7):4049–59.

34. Ming W, Zuo J, Han J, Chen J. The impact of comorbid allergic airway disease on the severity and mortality of COVID-19: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2022;279(4):1675–90.

35. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2022;62(5):1308–16.

36. Pillay J, Rahman S, Guitard S, Wingert A, Hartling L. Risk factors and preventive interventions for post Covid-19 condition: systematic review. Emerg Microbes Infect. 2022 Dec;11(1):2762–80.

37. Shams M, Basati G, Kalvandi G, Abdoli A, Tavan H. Frequency of underlying diseases, symptoms and mortality rate of COVID-19: a systematic review and meta-analysis. Rev Res Med Microbiol. 2022 Jan;33(1):e189.

38. Raeisi T, Mozaffari H, Sepehri N, Darand M, Razi B, Garousi N, et al. The negative impact of obesity on the occurrence and prognosis of the 2019 novel coronavirus (COVID-19) disease: a systematic review and meta-analysis. Eat Weight Disord EWD. 2022 Apr;27(3):893–911.

39. Rottler M, Ocskay K, Sipos Z, Görbe A, Virág M, Hegyi P, et al. Clinical Frailty Scale (CFS) indicated frailty is associated with increased in-hospital and 30-day mortality in COVID-19 patients: a systematic review and meta-analysis. Ann Intensive Care. 2022 Feb 20;12:17.

40. Roy S, Demmer RT. Impaired glucose regulation, SARS-CoV-2 infections and adverse COVID-19 outcomes. Transl Res. 2022 Mar;241:52–69.

41. Subramaniam A, Shekar K, Afroz A, Ashwin S, Billah B, Brown H, et al. Frailty and mortality associations in patients with COVID-19: a systematic review and meta-analysis. Intern Med J. 2022 May;52(5):724–39.

42. Sunjaya AP, Allida SM, Di Tanna GL, Jenkins CR. Asthma and COVID-19 risk: a systematic review and meta-analysis. Eur Respir J. 2022 Mar;59(3):2101209.

43. Szarpak L, Filipiak KJ, Skwarek A, Pruc M, Rahnama M, Denegri A, et al. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: A systematic review and meta-analysis. Cardiol J. 2022;29(1):33–43.

44. Wang Z, Joshi A, Leopold K, Jackson S, Christensen S, Nayfeh T, et al. Association of vitamin D deficiency with COVID-19 infection severity: Systematic review and meta-analysis. Clin Endocrinol (Oxf). 2022 Mar;96(3):281–7.

45. Zaboli R, Mousavi SM, Bahadori M, Mehdizadeh P, Asgharzadeh A, Delavari A. Influential Factors on the Hospitalization Length of COVID-19 patients: A Systematic Review. Trauma Mon. 2022 Jan 1;27(Especial Issue (COVID-19 and Emergency Medicine)):82–99.

46. Harwood R, Yan H, Talawila Da Camara N, Smith C, Ward J, Tudur-Smith C, et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. EClinicalMedicine. 2022 Feb;44:101287.

47. Widjanarko MW, Nindya M, Fernandez G, Jovito A. Comorbidities and COVID-19 severity in pediatric patients: systematic review and meta-analysis. Paediatr Indones. 2022 Feb 18;62(1):51–60.

48. Oliveira da Silva Kist ML, Hanzen Andrades GR, Drumond Costa CA, Crestani F, Ramos Garcia PC. Weight excess association with severity in children and adolescents with COVID-19: A systematic review. Clin Nutr Espen. 2022 Jun;49:114–20.

49. Mongkonsritragoon W, Prueksapraoprong C, Kewcharoen J, Tokavanich N, Prasitlumkum N, Huang J, et al. Prevalence and risk associated with asthma in children hospitalized with SARS-CoV-2: a meta-analysis and systematic review. J Allergy Clin Immunol Pract. 2022 May;10(5):1382-1384.e1.

50. Choi JH, Choi SH, Yun KW. Risk Factors for Severe COVID-19 in Children: A Systematic Review and Meta-Analysis. J Korean Med Sci. 2022 Feb 7;37(5):e35.

51. Impact of cancer diagnoses on the outcomes of patients with COVID-19: a systematic review and meta-analysis - PubMed [Internet]. [cited 2023 May 22]. Available from: https://pubmed.ncbi.nlm.nih.gov/35131810/

52. Zou Y, Han M, Wang J, Zhao J, Gan H, Yang Y. Predictive value of frailty in the mortality of hospitalized patients with COVID-19: a systematic review and meta-analysis. Ann Transl Med. 2022 Feb;10(4):166.

53. Szarpak L, Mierzejewska M, Jurek J, Kochanowska A, Gasecka A, Truszewski Z, et al. Effect of Coronary Artery Disease on COVID-19-Prognosis and Risk Assessment: A Systematic Review and Meta-Analysis. Biology. 2022 Jan 29;11(2):221.

54. Mude W, Oguoma VM, Nyanhanda T, Mwanri L, Njue C. Racial disparities in COVID-19 pandemic cases, hospitalisations, and deaths: A systematic review and meta-analysis. J Glob Health. 2021 Jun 26;11:05015.

55. Racial and Ethnic Disparities in COVID-19–Related Infections, Hospitalizations, and Deaths: A Systematic Review: Annals of Internal Medicine: Vol 174, No 3 [Internet]. [cited 2023 May 22]. Available from: https://www.acpjournals.org/doi/full/10.7326/M20-6306

56. Magesh S, John D, Li WT, Li Y, Mattingly-app A, Jain S, et al. Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Nov 11;4(11):e2134147.

57. Tracking SARS-CoV-2 variants [Internet]. [cited 2023 Jan 6]. Available from: https://www.who.int/activities/tracking-SARS-CoV-2-variants

58. Chen S, Zhang Z, Yang J, Wang J, Zhai X, Bärnighausen T, et al. Fangcang shelter hospitals: a novel concept for responding to public health emergencies. The Lancet. 2020 Apr 18;395(10232):1305–14.

59. Munblit D, Nicholson T, Akrami A, Apfelbacher C, Chen J, De Groote W, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. Lancet Respir Med. 2022 Jul 1;10(7):715–24.

60. Stephenson T, Allin B, Nugawela MD, Rojas N, Dalrymple E, Pereira SP, et al. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. Arch Dis Child. 2022 Jul 1;107(7):674–80.

61. Williamson AE, Tydeman F, Miners A, Pyper K, Martineau AR. Short-term and long-term impacts of COVID-19 on economic vulnerability: a population-based longitudinal study (COVIDENCE UK). BMJ Open. 2022 Aug 23;12(8):e065083.

62. Treskova-Schwarzbach M, Haas L, Reda S, Pilic A, Borodova A, Karimi K, et al. Pre-existing health conditions and severe COVID-19 outcomes: an umbrella review approach and meta-analysis of global evidence. BMC Med. 2021 Aug 27;19(1):212.

63. Wang SV, Pinheiro S, Hua W, Arlett P, Uyama Y, Berlin JA, et al. STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. BMJ. 2021 Jan 12;372:m4856.

64. ENCePP Home Page [Internet]. [cited 2023 Jan 6]. Available from: https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

65. Guidelines for Good Pharmacoepidemiology Practices (GPP) - International Society for Pharmacoepidemiology [Internet]. [cited 2023 Jan 6]. Available from: https://www.pharmacoepi.org/resources/policies/guidelines-08027/

66. Raynaud M, Zhang H, Louis K, Goutaudier V, Wang J, Dubourg Q, et al. COVID-19-related medical research: a meta-research and critical appraisal. BMC Med Res Methodol. 2021 Jan 4;21(1):1.

67. El-Menyar A, Mekkodathil A, Asim M, Consunji R, Rizoli S, Abdel-Aziz Bahey A, et al. Publications and retracted articles of COVID-19 pharmacotherapy-related research: A systematic review. Sci Prog. 2021;104(2):368504211016936.

68. Capodici A, Salussolia A, Sanmarchi F, Gori D, Golinelli D. Biased, wrong and counterfeited evidences published during the COVID-19 pandemic, a systematic review of retracted COVID-19 papers. Qual Quant [Internet]. 2022 Nov 29 [cited 2023 Jan 6]; Available from: https://doi.org/10.1007/s11135-022-01587-3

69. Accorsi EK, Qiu X, Rumpler E, Kennedy-Shaffer L, Kahn R, Joshi K, et al. How to detect and reduce potential sources of biases in studies of SARS-CoV-2 and COVID-19. Eur J Epidemiol. 2021 Feb 1;36(2):179–96.

Figure Legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

Figure 2. Distribution of predictors and risk factors across the included SLRs

Figure 3. Common methodological challenges when identifying the role of COVID-19 predictors and risk factors in systematic literature reviews

Supplemental Information

Supplemental Material

Table 1. Evidence Mapping of The Most Reported Predictor/Risk Factors for Mortality, Hospitalisation, ICU admission and Post-COVID as presented in SLRs published between January and April 2022

	Mortality		**Hospitalisation**		**ICU admission**		**Long COVID@**	
	Adults	***Children***	***Adults***	***Children***	***Adults***	***Children***	***Adults***	***Children***
Age	Older age as a risk factor	Neonates, <1 years old as risk factors	Readmission					
Gender	Being male as a risk factor				Being male as a risk factor		Being female as a risk factor	
Ethnicity								Inconclusive
Socioeconomic position								Inconclusive
Smoking								
Cardiological disease								
Uncontrolled hypertension								
Gastrointestinal								
Asthma								
Respiratory/ chronic pulmonary disease								

Cancer								
Neurological								
Haematological								
Chronic kidney disease								
Diabetes			Both first admission and readmission					
Obesity								Inconclusive
Frailty	*	NA		NA		NA		NA
Vitamin D deficiency	^							

Colour coded explanations: cell highlighted in green; consistent statistically significant associations between predictors/ risk factors and COVID-19 outcomes; cell highlighted in yellow; inconsistent results reported among multiple studies, cell highlighted in red; consistent non-significant associations between predictor/ risk factors and COVID-19 outcomes; grey: when the authors of the SLRs reported that results were inconclusive. Empty cells notes that no relevant information was presented in included SLRs.

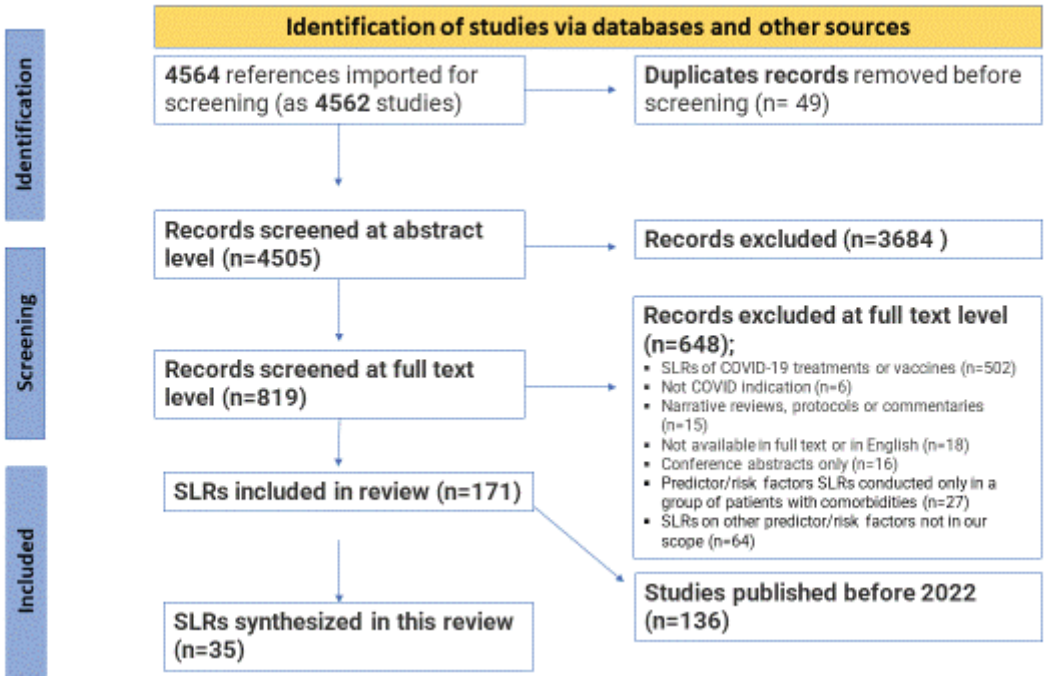
@ long COVID" defined as ongoing symptoms in individuals with a history of SARS-CoV-2 infection, lasting for at least 2 months following initial recovery that cannot be explained by an alternative diagnosis

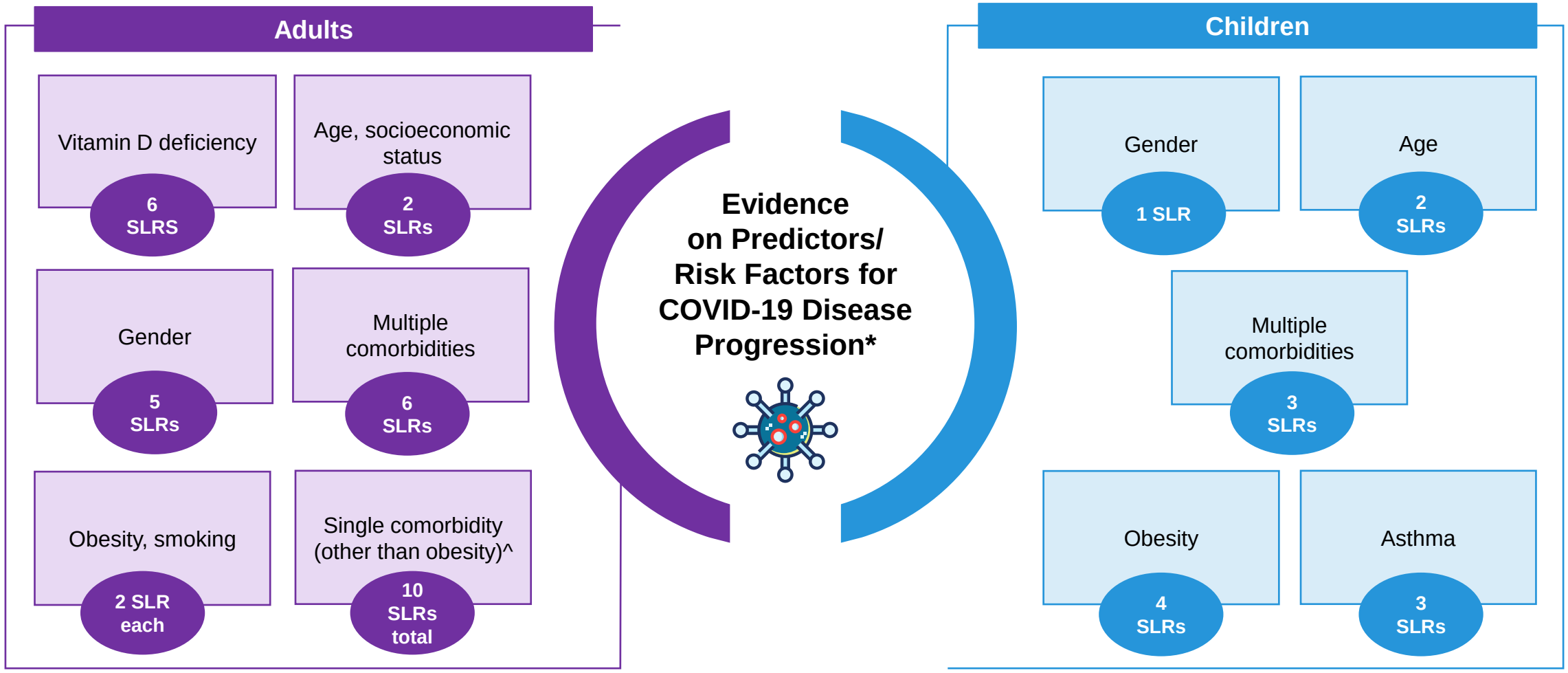
^The largest meta-regression found a significant association between vitamin D deficiency and mortality which was lost in sensitivity analyses excluding publications of high risk of bias, studies reporting unadjusted ORs and those with extreme effect estimates

*3 SLRs presented results for the association between frailty and mortality. 2 SLRs found positive associations whereas the third which adjusted for age, found no difference in short-term mortality between frail and non-frail COVID-19 patients

Table 2. Evidence from SLRs on racial and ethnic disparities in COVID-19 disease severity published in 2021

Authors	Title	Review Criteria	Summary of included studies	Summary Results
Mangesh, 2021	Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status: A Systematic-Review and Meta-analysis	Multiple databases published from January 1, 2020, to January 6, 2021.	A total of 4,318,929 patients from 68 US studies were included in the meta-analysis.	In age- and sex-adjusted analyses, Asian American individuals had the highest risk of intensive care unit admission. The area deprivation index was significantly associated with mortality rates in Asian American and Hispanic individuals. Decreased access to clinical care was positively significantly correlated with COVID-19 positivity in Hispanic individuals and African American individuals.
Mude, 2021	Racial disparities in COVID-19 pandemic cases, hospitalisations, and deaths: A systematic review and meta-analysis	Multiple databases were searched for SLRs published between January 2020 to April 2021 were included	72 studies were included, of which 75% were from USA and 18.1% from UK.	Black and Hispanic individuals experienced a significantly higher burden of COVID-19 (mortality, hospitalisation) compared to White individuals which remained following correction for publication bias. Intercountry differences were also observed regarding prevalence ratios of COVID-19.
Mackey, 2021	Racial and ethnic disparities in covid-19-related infections, hospitalizations, and deaths a systematic review	Multiple databases were searched for English SLRs publications from inception through August 2020	All studies were based in US settings; 37 mostly fair-quality cohort and cross-sectional studies, 15 mostly good-quality ecological studies, and data from the Centers for Disease Control and Prevention and APM Research Lab were included.	African American/Black and Hispanic populations experience disproportionately higher rates of hospitalization, and COVID-19–related mortality compared with non-Hispanic White populations, but not higher case- fatality rates (mostly reported as in-hospital mortality) (moderate- to high-strength evidence). Asian populations experience similar outcomes to non-Hispanic White populations (low-strength evidence). Outcomes for other racial/ethnic groups have been insufficiently studied.


Identification
Screening
Included
Identification of studies via databases and other sources
4564 references imported for screening (as 4562 studies)
Duplicates records removed before screening (n= 49)
Records screened at abstract level (n=4505)
Records excluded (n=3684)
Records screened at full text level (n=819)
Records excluded at full text level (n=648);
SLRs of COVID-19 treatments or vaccines (n=502)
Not COVID indication (n=6)
Narrative reviews, protocols or commentaries (n=15)
Not available in full text or in English (n=18)
Conference abstracts only (n=16)
Predictor/risk factors SLRs conducted only in a group of patients with comorbidities (n=27)
SLRs on other predictor/risk factors not in our scope (n=64)
SLRs included in review (n=171)
Studies published before 2022 (n=136)
SLRs synthesized in this review (n=35)

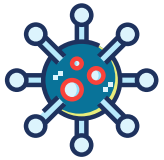


*The same SLR can appear in multiple boxes.
^Asthma, frailty, allergic airway disease, Parkinson's disease, cancer, diabetes, atrial arrhythmias, coronary artery disease,
Abbreviation: SLR, systematic literature review

Methodological Challenges on Predictor/Risk Factors Reviews

- **<u>Selection bias:</u> due to patients' selective risk profile**
  - Inconsistency in defining the predictor/risk factors, standardization of thresholds and outcomes definition
- **<u>Confounding bias</u>: differential distribution of causal risk factors**
  - Robust identification of confounders collected before the experience of disease
  - Lack of population-based studies with adequate patient representation
- **<u>Publication bias</u>: studies with significant results more likely to be published**

Evidence on Predictors/ Risk Factors for COVID-19 Disease Progression



Methodological Challenges on COVID-19 Predictor/Risk Factor Reviews

- Patients with comorbidities more likely to be selected for COVID-19 research
- Lack of understanding of socioeconomic impact including ethnicity on disease progression
- Data collection periods may reflect different disease patterns
- Temporality between factors and outcome assessments
- Lack of appropriate (adjusted) analyses to demonstrate causal relationships

Supplementary Files

Supplementary File 1_Protocol

Umbrella review of randomized and non-randomized study data in health care decision-making: a case-study of COVID-19 real world evidence

Luke Zabotka, Ravinder Claire, Grace Wangge, Andreas Freitag, Jamie Elvidge, Dalia Dawoud, Grammati Sarri

Citation

Luke Zabotka, Ravinder Claire, Grace Wangge, Andreas Freitag, Jamie Elvidge, Dalia Dawoud, Grammati Sarri. Umbrella review of randomized and non-randomized study data in health care decision-making: a case-study of COVID-19 real world evidence. PROSPERO 2022 CRD42022325761 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022325761

Review question

As part of illustrating the appropriate use of an International Society for Pharmacoepidemiology (ISPE)-endorsed framework for the incorporation of evidence from high-quality non-randomized studies alongside randomized controlled trials (RCTs) for clinical decision related to COVID-19, we aim to conduct an umbrella review of previously published systematic literature reviews, meta-analyses, and network meta-analyses on pharmacological treatments and vaccines for COVID-19 based on evidence from clinical trials and comparative observational, real-world evidence studies. Depending on the results of the identified reviews, we may consider updating the most recent and methodologically sound review. This protocol covers both types of reviews (umbrella review of systematic reviews, reviews of primary studies).

Searches

We will search for studies in the following electronic databases (all via Ovid): MEDLINE and MEDLINE In-Process, Embase, EBMR HTA, LitCovid (NCBI-NLM-NIH), Cochrane Library, MedRxiv, and WHO COVID-19 Research Database. Other sources will include PROSPERO or other systematic literature review registries and Grey literature from Health Technology Agencies. Searches will be conducted from 2020 onward.

Types of study to be included

Inclusion:

Systematic reviews (including living reviews) meta-analyses, and network meta-analyses of RCTs and/or observational studies.

Exclusion:

Primary studies, narrative reviews and scoping reviews, and publications unavailable in English. We will also exclude systematic reviews of non-pharmacological treatments and public health measures to reduce virus transmission or reviews without a search protocol. We will not consider conference posters or abstracts as publications.

Condition or domain being studied

COVID-19 infection (novel 2019 SARS-CoV-2)

Participants/population

Any patient with a diagnosis of COVID-19 (independent of severity).

Intervention(s), exposure(s)

Any pharmacological intervention, including convalescent plasma, STEM cell treatment, and vaccines.

Comparator(s)/control

Other pharmacological treatments, placebo, standard of care, or no treatment.

Context

Included systematic reviews will include treatments received in an inpatient, outpatient, and Intensive Care Unit settings. Inclusion will not be restricted based upon demographics or disease severity. Depending on the results of the umbrella review, we may conduct secondary reviews pertaining to primary RCTs, primary non-randomized studies, or real world evidence comparative effectiveness studies.

Main outcome(s)

A composite of WHO core standardized outcomes and COMET initiative core outcomes, including:

- Viral burden (quantitative PCR threshold) including RT-PCR negativity
- Patient survival
- Disease progression
- Hospital length of stay
- Serious adverse events
- Nonmortal clinical outcomes including the following: organ dysfunction pulmonary function, biochemical parameters (arterial partial pressure of oxygen (PaO2) and oxygen concentration (FiO2)), radiological findings, secondary infections, quality of life, and pregnancy outcomes

Measures of effect

Effect measures that are reported in each individual review (e.g. mean difference, risk ratio, odds ratio)

Additional outcome(s)

Not applicable.

Data extraction (selection and coding) [1 change]

After the removing of duplicates across the databases using EndNote, the references will be uploaded to an online platform (Covidence) and the title and abstracts of the imported publications will be independently evaluated by two reviewers. Any discrepancy will be resolved by a senior reviewer (GS). After potential conflicts are resolved, full text screening will be performed following the same procedure (screened by two independent reviewers, with any conflicts being resolved by a third senior reviewer).

Once full-text screening has been completed, the following elements will be extracted in a pre-designed Excel worksheet. Each systematic review will be extracted by one reviewer and independently validated by a second reviewer for accuracy. The following elements will be extracted:

- Publication details
- Type of review (Systematic review of RCTs only, systematic review of both RCTs and observational studies, systematic review of observational studies only)
- Targeted population and subgroups

- Search criteria and limitations
- Searched databases
- Number of included studies in each systematic review
- Description of study design of included studies; grouping will be conducted by study design and elements of quality (for RCTs, the percentage of double blinded studies with appropriate randomization will be reported and for observational studies, elements of quality such as use of adjusted analyses and appropriate measurement of exposure and outcomes)
- Qualitative summary of results if no meta-analysis or network meta-analysis was performed
- Quantitative summary of results (effect estimates hazard ratios, odds ratios, with 95% confidence intervals)
- If a network meta-analysis is involved, additional statistical measures of heterogeneity will be extracted
- Limitations as reported by the authors

Risk of bias (quality) assessment

We will assess the methodological quality of the included systematic reviews using the AMSTAR 2 tool. The AMSTAR 2 checklist includes 16 items (7 of which are considered critical) to assess specific elements of the systematic reviews.

Strategy for data synthesis [1 change]

Once data extraction is completed, we will qualitatively synthesize the results across the included systematic reviews in a Word document. We aim to provide an evidence map by highlighting the evidence identified by each systematic review, their commonalities and differences based on their original scope and identify any evidence gaps from the previously published systematic reviews.

Analysis of subgroups or subsets

Subgroups of interest include adults aged 18 years or older, children, immunocompromised individuals, the elderly (greater than 75 years of age), and by disease severity (ICU or mechanical ventilation).

Contact details for further information

Ravinder Claire
ravinder.claire@nice.org.uk

Organisational affiliation of the review

Brigham and Women's Hospital and Harvard Medical School
National Institute for Health and Care Excellence (NICE)
Monash University, Indonesia
Cytel

Review team members and their organisational affiliations

Mr Luke Zabotka. Brigham and Women's Hospital and Harvard Medical School
Dr Ravinder Claire. National Institute for Health and Care Excellence
Dr Grace Wangge. Monash University, Indonesia
Dr Andreas Freitag. Cytel
Mr Jamie Elvidge. National Institute for Health and Care Excellence
Dr Dalia Dawoud. National Institute for Health and Care Excellence
Dr Grammati Sarri. Cytel

Type and method of review

Review of reviews, Systematic review, Other

Anticipated or actual start date

19 April 2022

Anticipated completion date

01 June 2022

Funding sources/sponsors

Funding from the International Society for Pharmacoepidemiology as part of the funded manuscripts programme agreement.

Conflicts of interest

None known

Language

English

Country

England, Indonesia, United States of America

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

COVID-19; Decision Making; Delivery of Health Care; Humans; SARS-CoV-2

Date of registration in PROSPERO

04 May 2022

Date of first submission

20 April 2022

Stage of review at time of this submission

The review has not started

Supplementary Table 1_List of Included SLRs Published in 2021

Title	Authors
Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis	Gungor, B. et al
Cardiovascular drugs and COVID-19 clinical outcomes: A living systematic review and meta-analysis	Asiimwe, Innocent G. et al

Polypharmacy among COVID-19 patients: A systematic review	Iloanusi, S. et al
Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: A systematic review, meta-analysis and call for action	Liu, L et al
Does taking an angiotensin inhibitor increase the risk for COVID-19? - a systematic review and meta-analysis	Ma, Z. et al
COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities	Williams, N. et al
Impact of Chronic Kidney Disease on Severity and Mortality in COVID-19 Patients: A Systematic Review and Meta-analysis	Menon, Trishala et al
D-dimer, disease severity, and deaths (3D-study) in patients with COVID-19: a systematic review and meta-analysis of 100 studies	Varikasuvu, Seshadri Reddy et al
Delirium is a good predictor for poor outcomes from coronavirus disease 2019 (COVID-19) pneumonia: A systematic review, meta-analysis, and meta-regression	Hariyanto, Timotius Ivan et al
Dementia as a mortality predictor among older adults with COVID-19: A systematic review and meta-analysis of observational study	Saragih, Ita Daryanti et al
Outcomes among patients with COVID-19 and asthma: A systematic review and meta-analysis	Sitek, Andrea N. et al
COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis	Chang, R. et al
Hypertension as a prognostic factor in the prediction of mortality in patients with COVID-19: A systematic review and meta-analysis	Pagdanganan, C. D. P. and Juangco, J.
Meta-analysis investigating the relationship between clinical features, outcomes, and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia	Li, J.; He, X. et al
The association between Vitamin D and severity in Covid-19 patient: systematic review	Law, N. K et al
Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review	Yisak, Hiwot; et al
The J-Shaped Relationship Between Body Mass Index and Mortality in Patients With Covid-19: A Systematic Review and Dose-Response Meta-Analysis	Bukhari, Khulood et al
Cardiovascular risk factors, cardiovascular disease, and COVID-19: An umbrella review of systematic reviews	Harrison, S. L. et al
Hospitalised versus outpatient COVID-19 patients' background characteristics and comorbidities: A systematic review and meta-analysis	Mattey-Mora, et al
Accumulating Impact of Smoking and Co-morbidities on Severity and Mortality of COVID-19 Infection: A Systematic Review and Meta-analysis	Kumar, R. et al
Effect of Vitamin D Deficiency on COVID-19 Status: A Systematic Review	Das, Pranta et al
SARS-CoV-2 and Obesity: "CoVesity"-a Pandemic Within a Pandemic	Zakka, Kimberley et al
Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and COVID-19 severity: A systematic review and meta-analysis	Crafa, A et al
Risk factors for Covid-19 severity and fatality: a structured literature review	Wolff, D et al
Effect modification of the association between comorbidities and severe course of COVID-19 disease by age of study participants: a systematic review and meta-analysis	Fernandez Villalobos et al
Prognostic role of metabolic syndrome in covid-19 patients: A systematic review meta-analysis	Zuin, M. et al
Human immunodeficiency virus and mortality from coronavirus disease 2019: A systematic review and meta-analysis	Hariyanto, T. I. et al
Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis	Vai, B. et al
Thyroid disease and hypothyroidism are associated with poor COVID-19 outcomes: A systematic review, meta-analysis, and meta-regression	Damara, Fachreza et al
Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status: A Systematic-Review and Meta-analysis	Magesh, S et al.
Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients	Dessie, Zelalem G. et al
Prognostic role of anemia in COVID-19 patients: A Meta-analysis	Zuin, M. et al
Risks of infection, hospital and ICU admission, and death from COVID-19 in people with asthma: systematic review and meta-analyses	Otunla, A et al
Racial disparities in COVID-19 pandemic cases, hospitalisations, and deaths: A systematic review and meta-analysis	Mude, William et al
Diabetes and Risk of COVID-19 Mortality: A Systematic Review and Meta-Analysis	Kandil, Hend et al
Parkinson's disease may worsen outcomes from coronavirus disease 2019 (COVID-19) pneumonia in hospitalized patients: A systematic review, meta-analysis, and meta-regression	Putri, Cynthia et al
Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis	Biswas, M et al
Association of frailty with outcomes in individuals with COVID-19: A living review and meta-analysis	Dumitrascu, Flavia et al

Impact of diabetes mellitus on in-hospital mortality in adult patients with COVID-19: a systematic review and meta-analysis	Kaminska, Halla et al
The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis	Romero Starke et al
Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review	Cabrera Martimbianco, et al
Dementia and the risk of death in elderly patients with COVID-19 infection: Systematic review and meta-analysis	Zuin, M. et al
Cardiovascular, cerebrovascular, and renal co-morbidities in COVID-19 patients: A systematic-review and meta-analysis	Lee, Abby C. et al
A systematic review and meta-analysis of regional risk factors for critical outcomes of COVID-19 during early phase of the pandemic	Kim, Hyung-Jun; et al
Age-related risk factors and severity of SARS-CoV-2 infection: a systematic review and meta-analysis	Rahman, Mohammad et al
Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity and mortality of COVID-19: a rapid systematic review	Katoto, P. D. M. C et al
Smoking and risk of negative outcomes among COVID-19 patients: A systematic review and meta-analysis	Umnuaypornlert, Adinat et al
Hypertension is a clinically important risk factor for critical illness and mortality in COVID-19: A meta-analysis	Du, Yanbin et al
Factors associated with mortality in patients with COVID-19 admitted to intensive care: a systematic review and meta-analysis	Taylor, E. H. et al
Cardiovascular risk factors and mortality in hospitalized patients with covid-19: Systematic review and meta-analysis of 45 studies and 18,300 patients	Esposito, L. et al
Smoking Is Independently Associated With an Increased Risk for COVID-19 Mortality: A Systematic Review and Meta-analysis Based on Adjusted Effect Estimates	Hou, Hongjie; et al
COVID-19 and obesity: a systematic review and meta-analysis on the pre-existing clinical conditions, COVID-19 symptoms, laboratory findings and clinical outcomes	Rosv°rio Ferreira, et al
Are patients with coronavirus disease 2019 and obesity at a higher risk of hospital and intensive care unit admissions? A systematic review and meta-analysis	Wicaksana, A. L et al
Risk factors for poor outcomes in hospitalised COVID-19 patients: A systematic review and meta-analysis	Li, Y.; Ashcroft, T et al
Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis	Li, Xinyang et al
Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies	Mahamat-Saleh, Yahy et al
Obesity and Mortality Among Patients Diagnosed With COVID-19: A Systematic Review and Meta-Analysis	Poly, T. N.; et al
Coronavirus (COVID-19): A Systematic Review and Meta-analysis to Evaluate the Significance of Demographics and Comorbidities	Bhattacharyya, Arinjita; et al
What is the relationship between validated frailty scores and mortality for adults with COVID-19 in acute hospital care? A systematic review	Cosco, Theodore D.; et al
Can we predict the severe course of COVID-19 - a systematic review and meta-analysis of indicators of clinical outcome?	Katzenschlager, Stephan et al
Chronic Diseases as a Predictor for Severity and Mortality of COVID-19: A Systematic Review With Cumulative Meta-Analysis	Geng, JinSong; et al
Impact of metabolic and cardiovascular disease on COVID-19 mortality: A systematic review and meta-analysis	Sahni, Shubham et al
Prevalence of comorbidities among individuals with COVID-19: A rapid review of current literature	Bajgain, Kalpana Thapa; et al
Impact of cardiovascular disease on clinical outcomes in hospitalized patients with Covid-19: a systematic review and meta-analysis	Maddaloni, Ernesto; et al
Covid-19 and non-communicable diseases: evidence from a systematic literature review	Nikoloski, Zlatko; et al
A Systematic Review and Meta-Analysis of Risk Factors Associated with Severity and Death in COVID-19 Patients	Du, P.et al
Factors Associated for Mortality of Older People With COVID 19: A Systematic Review and Meta-analysis	Damayanthi, H. D. W. T.; et al
A meta-meta-analysis: Evaluation of meta-analyses published in the effectiveness of cardiovascular comorbidities on the severity of COVID-19	Naeini, M. B.; et al.
COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis	Gerayeli, F. V et al.
Pre-existing COPD is associated with an increased risk of mortality and severity in COVID-19: a rapid systematic review and meta-analysis	Rabbani, G.; et al
Effect of comorbid pulmonary disease on the severity of COVID-19: A systematic review and meta-analysis	GvºIsen, Askin; et al
Association of smoking and cardiovascular disease with disease progression in COVID-19: A systematic review and meta-analysis	Kang, Shiwei; et al
Dyslipidaemia and mortality in COVID-19 patients: a meta-analysis	Zuin, M.; et al
Serum HDL-c and LDL-c levels as the predictors of COVID-19 severity	Witarto, A. P.; et al

Pre-existing atrial fibrillation is associated with increased mortality in COVID-19 Patients	Zuin, M.; et al
Prediabetes and COVID-19 severity, an underestimated risk factor: A systematic review and meta-analysis	Heidarpour, Maryam; A et al
RISK FACTORS FOR COVID-19 RELATED MORTALITY- A SYSTEMATIC REVIEW AND META-ANALYSIS OF 26 STUDIES AND 9690 PATIENTS	Goel, Sunny Saxena Damini Johal et al
The Role of Nutrition in COVID-19 Susceptibility and Severity of Disease: A Systematic Review	James, Philip T.; et al
Prognostic implication of hypocalcaemia in COVID-19: A systematic review	Azeez, T. A.; et al
Cumulative Evidence for the Association of Thrombosis and the Prognosis of COVID-19: Systematic Review and Meta-Analysis	Xiao, Dongqiong et al
Prevalence and impact of atrial fibrillation in hospitalized patients with covid-19: A systematic review and meta-analysis	Romiti, G. F.; C et al
Racial and ethnic disparities in covid-19-related infections, hospitalizations, and deaths a systematic review	Mackey, K.; et al
Asthma in patients with coronavirus disease 2019: A systematic review and meta-analysis	Shi, L.; et al
Asthma does not increase COVID-19 mortality and poor outcomes: A systematic review and meta-analysis	Soeroto, Arto Yuwono; et al
Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies	Pijls, Bart G.; et al
A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19	Rafique, Z.; et al
The Impact of Vitamin D Deficiency on the Severity of Symptoms and Mortality Rate among Adult Patients with Covid-19: A Systematic Review and Meta-Analysis	Al Kiyumi, Maisa Hame et al
Smoking is associated with worse outcomes of COVID-19 particularly among younger adults: a systematic review and meta-analysis	Patanavanich, Roengrudee; et al
The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7)	Simons, D.; et al
Venous thromboembolism is linked to severity of disease in COVID-19 patients: A systematic literature review and exploratory meta-analysis	Srivastava, Rashmi et al
SARS-CoV-2 shedding dynamics across the respiratory tract, sex, and disease severity for adult and pediatric COVID-19	Chen, Paul Z et al
Frailty as a predictor of mortality among patients with COVID-19: a systematic review and meta-analysis	Zhang, X. M.; et al
Frailty as a mortality predictor in older adults with COVID-19: A systematic review and meta-analysis of cohort studies	Saragih, Ita Daryanti; et al
Factors Associated with Mortality among Elderly People in the COVID-19 Pandemic (SARS-CoV-2): A Systematic Review and Meta-Analysis	Alves, Vicente Paulo; et al

Supplementary Table 2. Main Characteristics of the 35 Included SLRs and their included studies published between January and April 2022

Study/First Author	Latest search cut-off date	Population	COVID-19 diagnosis	Predictors/ Risk Factors	Predictor(s) clearly defined (Y/N)	Clinical Outcomes	Outcome(s) clearly defined (Y/N)	Studies baseline information (country, age, gender, ethnicity)	Countries of included studies	Prospero Registration	Quality Assessment tool for NRS
Akbari 2022	September 25, 2021	NR	NR	Comorbidities, age, gender	N	Re-admissions (30-day, overall hospitalisations)	Y	All	Australia, China, Germany, Ireland, Israel, Italy, South Korea, Spain, Turkey, USA	N	JBI tool
Alzoughool 2022	July 18, 2020	Adults	NR	Comorbidities	N	Disease severity (composite outcome), mortality	N	Gender, ethnicity not reported	China, Italy, USA	Y	QUIPS tool
Baker 2022^	February 20, 2021	Adults	Laboratory confirmed	Smoking	Y	Disease severity, hospitalization, ICU admission, mechanical ventilation	Y	Only country	Bangladesh, Brazil, China, Egypt, India, Iraq, Israel, Italy, Kuwait, Mexico, Saudi Arabia, UK, USA	N	NR
Bellou 2022	July 26, 2020	All	Confirmed by RT-PCR or standardized clinical/radiological criteria	Demographics, comorbidities	Y	Hospitalization, mortality, invasive mechanical ventilation, ICU admission	Y	Only country	China, France, Italy, Spain, UK, USA	N	QUIPS tool
Boden 2022^	January 31, 2021	Adults	NR	Diabetic retinopathy	Y	Disease severity (composite outcome)	Y	All reported	China, Belgium, England, France, Scotland	N	QUIPS tool
Choi 2022	August 25, 2021	Children	NR	Age, prematurity, obesity, genetic factors, comorbidities	N	Severe disease (intensive care unit admission, invasive mechanical ventilation, and/or death)	y	Only country and age	France, Iran, Italy, Turkey, UK, USA, and multi-national studies	N	ROBANS tool
Cinar 2022	December 31, 2020	NR	NR	Comorbidities	N	Mortality	N	None	NR	Y	Polit and Beck Criteria
Darvishzadeh 2022	December, 2021	Adults	NR	Hypertension, comorbidities, age, gender	N	Mortality	N	Only age, gender	NR	N	NR
Dissanayake 2022	May 30, 2021	Adults	NR	Vit D deficiency	Y	Severe disease, mortality	Y	All but ethnicity	72/ Algeria, Belgium, Brazil, China, Egypt, Germany, Greece, India, Indonesia, Iran, Israel, Italy, Mexico, Netherlands, Oman, Pakistan, Russia, Saudi Arabia, South Korea, Spain, Switzerland, Turkey, UAE, UK, USA	Y	Newcastle-Ottawa scale
El-Qushayri 2022	March, 2021	Adults	NR	Parkinson disease	Y	Hospitalisation, ICU admission, mortality	N	Only age, gender	China, Italy, Spain, UK, USA	N	NIH tool

Study/First Author	Latest search cut-off date	Population	COVID-19 diagnosis	Predictors/ Risk Factors	Predictor(s) clearly defined (Y/N)	Clinical Outcomes	Outcome(s) clearly defined (Y/N)	Studies baseline information (country, age, gender, ethnicity)	Countries of included studies	Prospero Registration	Quality Assessment tool for NRS
Fabiao, 2022	May 13, 2021	Adults	NR	Gender	Y	Severe disease, mortality	Y	Age	NR	Y	Qualitative but no scale
Halim 2022	August 6, 2021	Adults	NR	Vit D deficiency	Y	Disease severity, mortality	Y	Only country	China, India, Iran, Italy, Spain, USA, and other countries	N	Newcastle-Ottawa scale
Han 2022	December 31, 2020	All	RT- PCR or 2019 Novel COVID-19 Diagnostic Criteria	Cancer	Y	ICU admission, and/or mechanical ventilation, mortality	Y	All but ethnicity	Canada, China, France, Iran, Italy, South Korea, Spain, UK, USA	N	Newcastle-Ottawa scale
Harwood 2022	May 21, 2021	Hospitalised children and young people	Confirmed by RT-PCR	Age, sex, ethnicity, co-morbidity and socioeconomic deprivation.	Y	Severe disease (composite outcome)	Y		Brazil, Chile, China, Colombia, France, Germany, India, Iran, Italy, Kazakhstan, Peru, Qatar, Saudi Arabia, South Africa, South Korea, Spain, Turkey, UK, USA	Y	Newcastle-Ottawa scale
Hu 2022	May 1, 2021	Adults	NR	Vit D deficiency	N	Mortality, ICU admissions, ventilator support, and length of hospital stay	N	Only country	China, Germany, Greece, India, Iran, Italy, Pakistan, Spain, Switzerland, Thailand, Turkey, UK, USA	Y	No (authors said that all NRs are of high risk of bias)
Jordan 2022^	30 November, 2020	Adults	NR	Vit D deficiency	N	Hospitalisation, mortality	N	Only country	Belgium, Brazil, Canada, France, Germany, India, Iran, Israel, Italy, Spain, Switzerland, Turkey, UK, USA	N	NR
Li 2022	November 22, 2021	Adults	WHO standards	Stroke	y	Mortality	N	All but ethnicity	China, Denmark, France, Iran, Israel, Italy, Lebanon, Netherlands, Norway, Russia, Saudi Arabia, South Korea, Sweden, Spain, Turkey, UK, USA	N	NR
Maglietta 2022	September 30, 2021	Hospitalised Adults	NR	Gender, disease severity during the acute phase	**Y**	Post-covid (new or persisting symptoms 12 weeks after initial infection)	Y	All but ethnicity	Brazil, China, France, Italy, Netherlands, Russia, Spain	Y	QUIPS tool
Ming 2022	March 31, 2021	NR (majority adults)	RT-PCR	Allergic airway disease	Y	Severity disease, mortality	N	All but ethnicity	Argentina, Bangladesh, Belgium, China, France, Israel, Kuwait, Mexico, South Korea, Spain, Sweden, Switzerland, Turkey, UK, USA	Y	Newcastle-Ottawa scale

Study/First Author	Latest search cut-off date	Population	COVID-19 diagnosis	Predictors/ Risk Factors	Predictor(s) clearly defined (Y/N)	Clinical Outcomes	Outcome(s) clearly defined (Y/N)	Studies baseline information (country, age, gender, ethnicity)	Countries of included studies	Prospero Registration	Quality Assessment tool for NRS
Mongkonsritragoon 2022	March, 2021	Children	NR	Asthma	Y	Hospitalisation, ICU admission	Y	Age, gender, data collection years	Austria, Netherlands, Spain, Switzerland, Turkey, UAE, UK, USA	N	NR
Oliveira da Silva Kist 2022^	September, 2020	Children and adolescents	Clinically or laboratory confirmed	Obesity	Y	Mortality, severe disease	Y	Only age reported	China, France, Switzerland, USA	Y	Newcastle-Ottawa scale
Pereira 2022	October 9, 2020	Adults	NR	Vit D deficiency	N	Severity, mortality, hospitalisation	Y	All but ethnicity	Austria, Belgium, China, England, Germany, Indonesia, Iran, Ireland, Israel, Russia, South Korea, Spain, Switzerland, UK, USA, Various countries in South Asia	N	Research Triangle Institute Item Bank
Pillay 2022	August, 2021	All	Laboratory vs no laboratory	Age, gender	Y	Post-covid (non-recovery)	Y	All reported	China, Italy, Norway, Russia, Sweden, Switzerland, Turkey, UK, USA	Y	GRADE, JBI tool
Raeisi 2022	June 1, 2020	Adults	NR	Obesity	Y	Severe disease, hospitalization, ICU admission, need for mechanical ventilation, mortality	Y	All reported	Bolivia, China, France, Germany, Italy, Mexico, Singapore, Spain, UK, USA	Y	GRADE
Rottler 2022	September 24, 2021	Hospitalised Adults	Clinical, radiological or laboratory	Frailty	Y	All-cause mortality, 30-day mortality, hospitalisation, ICU admission	Y	All but ethnicity	Austria, Belgium, Brazil, Denmark, Egypt, France, Germany, India, Iran, Ireland, Israel, Italy, Japan, Libya, Malaysia, Mexico, Morocco, Netherlands, Norway, Poland, Portugal, Saudi Arabia, Spain, Sudan, Switzerland, Turkey, UK, USA	Y	QUIPS tool
Roy 2022^	June, 2021	Adults	NR	Impaired glucose regulation	Y	Mortality, hospitalisation	Y	All but ethnicity	Austria, Belgium, China, France, India, Iraq, Italy, Mexico, Netherlands, Singapore, Turkey, UK, USA	N	NR
Shams 2022	2020	Adults	NR	Comorbidities	N	Mortality	N	All but ethnicity	China, Taiwan	N	STROBE
Subramaniam 2022	July 15, 2021	Hospitalised Adults	RT-PCR or clinical	Frailty	Y	Short-term mortality (in hospital or within 30 days), ICU admission and need for IMV	Y	All reported	Belgium, Brazil, Cyprus, Egypt, France, Greece, Iraq, Italy, Libya, Netherlands, Poland, Saudi Arabia, Spain, Sudan, Sweden,	Y	Newcastle-Ottawa scale

Study/First Author	Latest search cut-off date	Population	COVID-19 diagnosis	Predictors/ Risk Factors	Predictor(s) clearly defined (Y/N)	Clinical Outcomes	Outcome(s) clearly defined (Y/N)	Studies baseline information (country, age, gender, ethnicity)	Countries of included studies	Prospero Registration	Quality Assessment tool for NRS
									Switzerland, Turkey, UK, USA		
Sunjaya 2022	July 11, 2021	Adults	RT-PCR	Asthma	Y	Hospitalisation from COVID-19, ICU admission, IMV, mortality	Y	All but ethnicity	Argentina, Australia, Belgium, Brazil, China, Denmark, France, Ghana, Iran, Israel, Kuwait, Mexico, Norway, South Africa, South Korea, Spain, Sweden, Turkey, UK, USA	Y	Newcastle-Ottawa scale
Szarpak 2022	October, 2021	Adults	NR	Atrial arrythmia	N	In- hospital mortality, in-hospital cardiovascular death or hospital- or ICU length of study	**Y**	All but ethnicity	Bangladesh, China, Denmark, Finland, France, India, Iran, Italy, Kuwait, Netherlands, Poland, South Korea, Turkey, UK, USA	N	ROBINS-1
Szarpak 2022	November 2, 2021	Adults	NR	Coronary artery disease	N	Mortality, severity, ICU admission	N	All but ethnicity	China, Iran, Israel, Italy, Saudi Arabia, South Korea, Spain, UK	N	ROBINS-1
Wang 2022	December 3, 2020	Adults	Laboratory-confirmed (PCR)	Vit D deficiency	Y	Hospitalisation, ICU admission, mortality	Y	All reported	Austria, Belgium, China, Germany, India, Iran, Italy, Pakistan, Spain, Switzerland, UK, USA	N	Newcastle-Ottawa scale (modified)
Widjanarko 2022	March, 2021	Children	Confirmed by RT-PCR	Obesity, comorbidities	N	Severe disease (composite outcome)	Y	Only age	Australia, Austria, Brazil, China, France, India, Iran, Italy, Kuwait, Spain, Turkey, UK, USA	Y	STROBE and JBI tools
Zaboli 2022^	November 10, 2020	All	NR	Comorbidities, socioeconomic factors	N	Hospitalisation	Y	All but ethnicity	Australia, Brazil, China, France, India, Italy, Turkey, UK, USA	N	Newcastle-Ottawa scale
Zou 2022	September 11, 2021	Hospitalised Adults	NR	Frailty	Y	All-cause mortality	Y	All except ethnicity	Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, Turkey, UK	N	Newcastle-Ottawa scale

^Reviews did not conduct any quantitative analysis (meta-analysis)

Supplementary Table 3. Main results from the Included SLRs with Meta-Analysed results published between January and April 2022

Study/First Author	Predictors/ Risk Factors	Number of patients/ studies	Severity	Hospitalisation	ICU admission	Mortality	Post-Covid	Meta-regression (Y/N)	Heterogeneity (I_2)	Authors comments on interpretation of results
Akbari 2022	Comorbidities, age, gender	NR/ 25 studies	NR	**Re-admission** Older age OR 1.52; 1.17–1.97, male OR 15; 1.04–1.28/ white race OR 1.26; 1.04–1.52/ Comorbidities: OR range 1.58 (diabetes) –2.56 (heart failure) (all significant)	NR	NR	NR	N	Range between 0 to 95%	The causes and periods of readmission were heterogeneous between studies.
Alzoughool 2022	Comorbidities	19,156/ 34 studies	CVD OR 4.1; 95% CI, 2.9 – 5.7/ hypertension OR 2.5; 1.9 –3.6/ coronary heart disease OR, 2.5; 1.7 to 3.8	NR	NR	CVD OR 6.1; 95% CI, 2.9 to 12.7/ hypertension OR 3.2; 95% CI 2.0 –5.0	NR	N (results of adjusted not presented)	NR	No significant publication bias was indicated. Most studies did not report the eligibility criteria and whether participants were recruited consecutively.
Bellou 2022	Demographics, comorbidities	NR / 428 studies	NR	Obstructive sleep apnoea OR 2.11; 95% CI 1.54–2.89/ history of venous thromboembolism OR 2.35; 95% CI 1.75–3.14	Female sex OR 0.53; 95% CI 0.46–0.59	Use of angiotensin-converting enzyme inhibitors, cancer, chronic liver disease, COPD, dementia, any immunosuppressive medication, peripheral arterial disease, pharyngalgia, rheumatological disease, smoking; all significant	NR	N	<50%	More than half of these associations presented a nominally significant effect, and only 16 of them provided strong evidence in terms of sample size, statistical significance, Consistency, and lack of small-study effects. sources of heterogeneity could not be adequately explored due to poor reporting in the majority of articles
Choi 2022 (children)	Age, prematurity, obesity, genetic factors, comorbidities	10 studies	Neonate (RR 2.69; 95% CI, 1.83–3.97), prematurity in young infants (RR, 2.00; 95% CI, 1.63–2.46),/ Obesity (RR, 1.43; 1.24–1.64), diabetes (RR, 2.26; 1.95–2.62), chronic lung disease other than asthma (RR, 2.62; 1.71–4.00), asthma (RR, 1.08; 0.98-1.20)/ heart disease (RR, 1.82; 1.58–2.09), neurologic disease (RR, 1.18; 1.05–1.33), and immunocompromised status (RR, 1.44; 1.01–2.04)	NR	NR	NR	NR	N	0-86%	The nature of the included studies and the definition of comorbidities in the studies were heterogeneous.

Study/First Author	Predictors/ Risk Factors	Number of patients/ studies	Severity	Hospitalisation	ICU admission	Mortality	Post-Covid	Meta-regression (Y/N)	Heterogeneity (I_2)	Authors comments on interpretation of results
Cinar 2022	Comorbidities (cerebrovascular disease, cardiovascular disease, chronic liver disease)	NR/ 24 studies	NR	NR	NR	Overall effect size: 2,092 (G.A; 1,697-2,595) (SS)	NR	N	NR	NR
Darvishzadeh 2022	Hypertension, comorbidities, age, gender	3,104/ 10 studies	NR	NR	NR	Older age: MD 11.89; 95% CI 10.27–13.51/ Female: OR 0.37, 0.21 −0.53/ Hypertension: logOR 0.99; 0.82–1.15, CVD: OR 1.0; 0.92− 1.84 Diabetes: OR, 0.81, 0.72 −1.27/ Respiratory OR 0.78, 0.64 −1.05 (all SS)	NR	N	Age: 72%, male: 52%, hypertension: 13%, CVD: 17%, diabetes: 18%, respiratory comorbidities: 15%	High heterogeneity between studies in the study of some variables.
Dissanayake 2022	Vit D deficiency	1,976,099/ 72 studies	OR 1.90; 95% CI 1.52-2.38	NR	NR	OR 2.07; 95% CI 1.28–3.35	NR	Y (Cut-off for vitamin D deficiency/ insufficiency, severe COVID-19 criteria, geographical setting of each study)	Severity: 81%, Mortality: 73%	Discrepancies in timing of vitamin D testing, definitions of severe COVID-19, and vitamin D deficiency/insufficiency partly explained the heterogeneity.
El-Qushayri 2022	Parkinson disease	13 studies	NR	MD: 2.69, 95% CI, −6.99–12.37	Pooled rate: 4.7% (95% CI: 1.56–14.16)	Pooled Rate 25.1%; 95% CI: 16.37–38.49	NR	N	Hospitalisation and ICU admission: 0%, mortality: 77%	Adjustment for age and other baseline demographics was not conducted. Factors such as the period and place where each study was conducted may have influenced the results.
Fabiao, 2022	Gender	Severity outcome: 12,513/ 46 studies Mortality outcome: 20,601/ 16 studies	Men RR 1.29; 95%CI 1.19 – 1.40	NR	NR	Men: RR 1.36; 95% CI 1.17–1.59	NR	Y (Age)	Severity: 48%, Mortality: 63%	Age was not an important cofactor modulating these effects
Halim 2022	Vit D deficiency	1424/11 studies	MD −5.02; 95% CI −11.6832–1.63	NR	NR	aOR 1.39; 95% CI 0.71–2.69	NR	Y(only for severity outcome)	Severity: 94%, mortality: 66%	Most studies were Chinese with potential location bias.
Han 2022	Cancer	63,413 / 57 studies	RR 1.49; 95% CI 1.18 – 1.87	NR	NR	RR 1.41; 95% CI 1.15 –1.73	NR	N	Severity: 67%, mortality: 97%	Heterogeneity and retrospective nature of the studies, including reporting and selection biases. A few studies were reported from the same hospitals and hence there may be overlapping patients.

Study/First Author	Predictors/ Risk Factors	Number of patients/ studies	Severity	Hospitalisation	ICU admission	Mortality	Post-Covid	Meta-regression (Y/N)	Heterogeneity (I_2)	Authors comments on interpretation of results
Harwood 2022 (children and young people)	Sociodemographic factors, comorbidities (number of comorbidities, cardiovascular, respiratory, asthma, gastrointestinal, neurological, malignancy, haematological, immunosuppression, obesity, obesity without comorbidity, trisomia 21)	21,549/ 83 studies	NR	NR	Male: OR 1.19 (95% CI 0.93 – 1.52)/ Infants (<1 year): OR 1.63; 95% CI 1.40–1.90/ Comorbidities OR range btw 1.07 (haematological) to 3.08 (immunosuppressants use and gastrointestinal) (comorbidities not statistical significantly related to the outcome: asthma, malignancy, haematological, immunosuppression)$	Male: OR 0.94; 95% CI 0.83–1.05 Infants (<1 year): OR 2.08, 1.57–2.86/ 10-14 years: OR 2.15 (1.54–2.98); >14 years OR 2.15 (1.61–2.88))/ Comorbidities OR range btw 1.70 (respiratory) to 13.17 (endocrine including diabetes) (comorbidities not statistical significantly related to the outcome: respiratory, asthma)$	NR	N (but IPD MA for some studies)	ICU admission: range 0 – 74%, mortality: range 0-73%	Included studies were highly heterogenous and from a wide range of resource settings; however across both the aggregate and IPD analyses, no association was found between sex and odds of severe disease or death. The odds of poor outcomes was 1.6 to 2-fold higher for infants than 1–4 year olds for COVID-19 alone, but teenagers had elevated odds of severe COVID-19 (1.4 to 2.2-fold higher odds). The presence of any comorbidity increased odds of severe COVID-19 for both t analyses (OR 2.56 (1.77, 3.71) and 1.64 (1.59, 1.69) respectively for critical care admission), increasing absolute risk of critical care admission by 4.5% (a relative increase of 28%) and risk of death by 2.5% (125% relative increase). It was not possible to assess the impact of ethnicity and socioeconomic position on clinical outcomes due to highly variable reporting.
Hu 2022	Vit D deficiency	12,806/ 20 studies	NR	MD 0.84; 95% CI -0.45–2.13	RR 0.87; 95% CI 0.67–1.14	RR 1.49; 95% CI 1.34–1.65	NR	N	Hospitalisation: 0% ICU admission: 0% Mortality: 83%	Variation in exposure definition, lack of information on prior Vit D products and on comorbidities may have impacted the findings.
Li 2022	Stroke	7,267,055/47 studies	NR	NR	NR	Pooled effect 1.30; 95% CI 1.16–1.44	NR	Y (measurement of effect type)	Mortality: 89%	Subgroup analyses yielded consistent results among area, age, proportion of males, setting, cases, effect type, and proportion of severe COVID-19 cases. Statistical heterogeneity might result from the different effect type across studies
Maglietta 2022	Sex, disease severity during the acute COVID-19 phase	13,340/ 20 studies	NR	NR	NR	NR	Female: OR 1.52; 95% CI 1.27–1.82, Acute disease severity: OR 1.66, 95% CI 1.03–2.68~	N	Female: 68%	Possible selection errors due to high loss to follow-up and/or the lack of comparison between participants and non-participants. Half of the studies were single-centred with no prior sample size calculation, and identification of prognostic factors was almost always a secondary objective. A meta-analysis of adjusted results was not possible due to different sets of adjustement factors
Ming 2022	Allergic airway disease	345,091/ 34 studies	OR 1.10; 95% CI, 0.90–1.35	NR	NR	OR 0.83; 95% CI 0.70–0.99	NR	N	Severity: 89%, mortality: 74%	Subgroup analysis indicated that severity results were not affected by differences in study designs, disease categories, countries, the definition of severity, and population size of AAD. However, mortality results were impacted by case numbers and study design.
Mongkonsritragoon 2022 (children)	Asthma	1,193/ 9 studies	NR	OR 0.79; 95% CI0.25-2.46	RR 0.82; 95% CI, 0.13-5.08	NR	NR	N	Hospitalisation: 83%, ICU admission: 67%	Differences in cut off age of paediatric patients across the studies, lack of information on asthma diagnosis, important covariates for adjustment (severity, types of treatment, phenotypes, comorbidities) were not considered

Study/First Author	Predictors/ Risk Factors	Number of patients/ studies	Severity	Hospitalisation	ICU admission	Mortality	Post-Covid	Meta-regression (Y/N)	Heterogeneity (I_2)	Authors comments on interpretation of results
Pereira 2022	Vit D deficiency	8,176/ 26 studies	OR 1.65; 95% CI 1.30–2.09	OR 1.81; 95% CI 1.41–2.21	NR	OR 1.82; 95% CI 1.06–2.58	NR	N	Severity: 36%, hospitalisation: 0%mortality: 59%	Results of the studies included in this review were not stratified by participants sex or the presence of comorbidities and most were of high risk of bias
Pillay 2022	Demographics, comorbidities	17 studies	NR	NR	NR	NR	Age (continuous): 0.99 (0.98 to 1.00), Female: 1.72 (1.53 to 1.94)*	Y (age, sex, COVID-19 severity, comorbidities)	Age: 48%, Gender: 0%	Variations in definition of post Covid-19 outcomes and timing of assessment make it difficult to draw conclusions
Raeisi 2022	Obesity	479,052/ 54 studies	OR=1.62; 95% CI 1.48–1.7	OR=1.75; 95% CI 1.47–2.09	OR=1.75; 95% CI 1.38–2.22	OR=1.23; 95% CI 1.06–1.41	NR	Y (sex, age)	Severity: 67%, Hospitalisation: 73.3%, ICU admission: 74%, Mortality: 63%	Meta-regression showed that the relationships between obesity and all outcomes were not affected by sex and age. Subgroup analyses showed that these relationships were independent of study design, age, level of covariate adjustments.
Rottler 2022	Frailty	NR / 42 studies	NR	OR: 0.83; 95% CI 0.63–1.09	NR	UK studies: OR 3.48; 95% CI 2.74 –4.42/ Non UK studies: OR 2.98; 2.31–3.83	NR	N	>95%	Heterogeneity, retrospective studies carried high risk of bias.
Shams 2022	Comorbidities	2,720/ 18 studies	NR	NR	NR	Hypertension: 41%, diabetes: 18%, CVD: 11% (all P<0.001)	NR	Y (gender, sample size, study collection years)	Mortality: range between 87-99%	Limited variables presented across studies
Subramaniam 2022	Frailty, gender	34 628/ 25 studies	NR	Non frailty RR 1.63; 95% CI: 1.30–2.03	NR	Male RR 1.08; 95% CI 1.06–1.11/ Frailty RR 1.04; 95% CI 0.84–1.28/ significant comorbidities (dementia, chronic kidney disease, heart failure, diabetes, hypertension, cerebrovascular accident)/ no difference by ethnicity, obesity, chronic respiratory disease	NR	Y (by age)	ICU admission: 89%, mortality: 99%	A few included studies had very small numbers of patients and multiple studies may have covered similar patient cohorts.
Sunjaya 2022	Asthma	965,551/ 51 studies	NR	RR 1.18; 95% CI 0.98–1.42	RR 1.21; 95% CI 0.97–1.51	RR 0.94; 95% CI 0.76–1.17	NR	Y	Hospitalisation: 99%, ICU admission: 94%, mortality: 95%	Subgroup analyses by continent revealed a significant difference in risk of acquiring COVID-19, ICU admission, ventilator use and death between the continents.
Szarpak 2022	Coronary artery disease	49,286/ 62 studies	OR = 2.28; 95% CI 1.59-3.27	NR	OR = 2.25; 95%CI: 1.34 to 3.79	OR = 0.33; 95%CI: 0.29–0.39	NR	N	Severity: 72%, ICU admission: 0, mortality: 70%	Variation in study methodology, most studies were retrospective in nature and suffered limitations related to its category, including missing data related to medical history. Since all the studies consisted of patients admitted to the hospital, there is a concern of overrepresentation of severe COVID-19 cases.

Study/First Author	Predictors/ Risk Factors	Number of patients/ studies	Severity	Hospitalisation	ICU admission	Mortality	Post-Covid	Meta-regression (Y/N)	Heterogeneity (I_2)	Authors comments on interpretation of results
Wang 2022	Vit D deficiency	2,757/17 studies	NR	OR 2.18; 95% CI 1.48–3.21	OR 5.44; 95% CI 0.38–78.42	OR 2.47; 95% CI 1.50–4.05	NR	N	Mortality: 30.5% Hospitalisation: 0% ICU admission: 83.1%	Most of the included studies did not adjust for any confounding variables (weight status, race and age) and the observed associations may not predict causality.
Widjanarko 2022 (children)	Obesity, comorbidities	285,828/ 41 studies	Any comorbidity OR 4.07 (95%CI 2.31 – 7.19)	NR	NR	NR	NR	N	88%	
Zou 2022	Frailty	26,652/21 studies	NR	NR	OR =0.5; 95% CI: 0.1–2.1	OR 2.8; 95% CI 2.3–3.5	NR	N	ICU admission: 89.4%, mortality: 78%	Most studies were retrospective and selection bias was present, some results across tools were pooled

Abbreviations: NR = not reported, Y = yes, N = no, OR = odds ratio, RR = risk ratio, MD = mean difference, aOR = adjusted odds ratio, SS = statistically significant

^ Became insignificant when studies with high risk of bias or studies reporting unadjusted effect estimates were excluded.

*Single studies reported results on association between obesity and post-Covid and found no statistically significant associations even though conclusions were very uncertain. One study was included for children which showed that age (continuous) and allergies may increase the risk of post-covid but not gender (female), obesity, pneumonia during acute COVID-19, and disease severity Results were very uncertain.

~ Post covid linked to respiratory symptoms

$ Results from aggregated data analyses

Supplementary Table 4_AMSTAR2 Quality assessment of Included SLRs Published in 2022

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Dissanayake, H. A.; de Silva, N. L.; Sumanatilleke, M.; de Silva, S. D. N.; Gamage, K. K. K.; Dematapitiya, C.; Kuruppu, D. C.; Ranasinghe, P.; Pathmanathan, S.; Katulanda, P.	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
FabiAo, J.; Sassi, B.; Pedrollo, E. F.; Gerchman, F.; Kramer, C. K.; LeitV£o, C. B.; Pinto, L. C.	Y	Y	N	N	Y	Y	N	N	N	N	Y	N	N	N	Y
Ferrara, P.; Gianfredi, V.; Tomaselli, V.; Polosa, R.	Y	N	Y	Y	Y	N	Y	Y	Y	N	NA	NA	N	N	NA
Jordan, Taja Siuka Darko Rotovnik Nada Kozjek Pfeifer Marija	Y	N	N	N	Y	N	N	Y	N	N	NA	NA	N	N	N
Raeisi, T.; Mozaffari, H.; Sepehri, N.; Darand, M.; Razi, B.; Garousi, N.; Alizadeh, M.; Alizadeh, S.	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y
Pillay, J.; Rahman, S.; Guitard, S.; Wingert, A.; Hartling, L.	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
Zaboli, R.; Mousavi, S. M.; Bahadori, M.; Mehdizadeh, P.; Asgharzadeh, A.; Delavari, A.	Y	N	N	N	Y	N	N	Y	Y	N	NA	NA	N	N	N
Wang, Zhen; Joshi, Avni; Leopold, Kaitlin; Jackson, Sarah; Christensen, Stephanie; Nayfeh, Tarek; Mohammed, Khaled; Creo, Ana; Tebben, Peter; Kumar, Seema	Y	N	N	N	Y	N	N	Y	Y	N	Y	N	N	N	Y
Baker, Jessica; Krishnan, Nandita; Abroms, Lorien C.; Berg, Carla J.	Y	N	N	Y	N	N	N	Y	N	N	NA	NA	N	Y	N
Pereira, Marcos; Dantas Damascena, Alialdo; GalvV£o Azevedo, Laylla Mirella; de Almeida Oliveira, Tarcio; da Mota Santana, Jerusa	Y	N	N	Y	Y	N	N	Y	Y	N	Y	N	Y	Y	Y
Hu, Y.; Kung, J. Y.; Cave, A.; Banh, H. L.	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	N	N	N	N
Mongkonsritragoon, Wimwipa; Prueksapraoprong, Chattip; Kewcharoen, Jakrin; Tokavanich, Nithi; Prasitlumkum, Narut; Huang, Jenny; Poowuttikul, Pavadee	Y	N	Y	Y	Y	N	N	Y	N	N	N	N	Y	Y	Y
Shams, M.; Basati, G.; Kalvandi, G.; Abdoli, A.; Tavan, H.	Y	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y
Ming, Wei; Zuo, Jingjing; Han, Jibo; Chen, Jinhui	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y
El-Qushayri, Amr Ehab; Ghozy, Sherief; Reda, Abdullah; Kamel, Ahmed Mostafa Ahmed; Abbas, Alzhraa Salah; Dmytriw, Adam A.	Y	N	N	N	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y
Li, Shuwen; Ren, Jiahao; Hou, Hongjie; Han, Xueya; Xu, Jie; Duan, Guangcai; Wang, Yadong; Yang, Haiyan	Y	N	N	Y	Y	N	N	Y	N	N	Y	N	N	Y	Y
Maglietta, Giuseppe; Diodati, Francesca; Puntoni, Matteo; Lazzarelli, Silvia; Marcomini, Barbara; Patrizi, Laura; Caminiti, Caterina	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y
Halim, Ceria; Mirza, Audrey Fabianisa; Sari, Mutiara Indah	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	N
Harwood, Rachel; Yan, Helen; Talawila Da Camara, Nishanthi; Smith, Clare; Ward, Joseph; Tudur-Smith, Catrin; Linney, Michael; Clark, Matthew; Whittaker, Elizabeth; Saatci, Defne; Davis, Peter J.; Luyt, Karen; Draper, Elizabeth S.; Kenny, Simon E.; Fraser, Lorna K.; Viner, Russell M.	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y
Widjanarko, M. W.; Nindya, M.; Fernandez, G.; Jovito, A.	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N	N
Choi, Jae Hong; Choi, Soo-Han; Yun, Ki Wook	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Oliveira da Silva Kist, Mayara LuV≠za Hanzen Andrades Gabriela Rupp Drumond Costa Caroline Abud Crestani Francielly Ramos Garcia Pedro Celiny	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N
Roy, S.; Demmer, R. T.	N	N	N	N	Y	N	Y	Y	N	Y	N	N	N	N	Y
Darvishzadeh, A.; Hasani, H.; Behrouzinezhad, R.; Bahmani, A.; Delavar, M.	N	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	Y	N
Váƒ±nar, F.; Cinar F; Ekinci, G.	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N
Akbari, Abolfazl; Fathabadi, Amirhossein; Razmi, Mahya; Zarifian, Ahmadreza; Amiri, Mahdi; Ghodsi, Alireza; Vafadar Moradi, Elnaz	N	N	Y	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	N
Alzoughool, Foad; Abumweis, Suhad; Alanagreh, Lo'ai; Atoum, Manar	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y
Boden, Isabel; Bernabeu, Miguel O.; Dhillon, Baljean; Dorward, David A.; MacCormick, Ian; Megaw, Roly; Tochel, Claire	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Zou, Yupei; Han, Maonan; Wang, Jiarong; Zhao, Jichun; Gan, Huatian; Yang, Yi	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Bellou, Vanesa; Tzoulaki, Ioanna; van Smeden, Maarten; Moons, Karel G. M.; Evangelou, Evangelos; Belbasis, Lazaros	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Szarpak, Lukasz; Filipiak, Krzysztof J.; Skwarek, Aleksandra; Pruc, Michal; Rahnama, Mansur; Denegri, Andrea; Jachowicz, Marta; Dawidowska, Malgorzata; Gasecka, Aleksandra; Jaguszewski, Milosz J.; Iskrzycki, Lukasz; Rafique, Zubaid	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N
Subramaniam, Ashwin; Shekar, Kiran; Afroz, Afsana; Ashwin, Sushma; Billah, Baki; Brown, Hamish; Kundi, Harun; Lim, Zheng Jie; Ponnapa Reddy, Mallikarjuna; Curtis, J. Randall	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Sunjaya, Anthony P.; Allida, Sabine M.; Di Tanna, Gian Luca; Jenkins, Christine R.	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y

Szarpak, Lukasz; Mierzejewska, Malgorzata; Jurek, Jonasz; Kochanowska, Anna; Gasecka, Aleksandra; Truszewski, Zenon; Pruc, Michal; Blek, Natasza; Rafique, Zubaid; Filipiak, Krzysztof J.; Denegri, Andrea; Jaguszewski, Milosz J.	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Han, Shuting; Zhuang, Qingyuan; Chiang, Jianbang; Tan, Sze Huey; Chua, Gail Wan Ying; Xie, Conghua; Chua, Melvin L. K.; Soon, Yu Yang; Yang, Valerie Shiwen	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	N	Y	Y