Cardiovascular Risk Factors, Cardiovascular Disease and COVID-19:

An Umbrella Review

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Stephanie L Harrison, Benjamin JR Buckley, José Miguel Rivera-Caravaca, Juqian Zhang and Gregory YH Lip

Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK

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Key messages

- An umbrella review is a review of systematic reviews or meta-analyses. This umbrella review aimed to answer: What is the association between cardiovascular risk factors or cardiovascular disease (CVD) and health outcomes, hospitalisation, mechanical ventilation and mortality caused by COVID-19? And What is the impact of COVID-19 on cardiovascular health?
- 84 systematic reviews were identified and appraised using AMSTAR 2; of these 52 reviews were assessed as critically low- or low-quality, 31 reviews were moderate quality and one review was high-quality. There was duplication of primary studies within the reviews, therefore the main findings from the largest, most recent, moderate quality review for each risk factor are highlighted, or from a high-quality review for smoking.
- **Cardiovascular disease (CVD)**: was associated with 3.9 times higher odds of severe COVID-19 and 2.7 times higher odds of mortality, although there may have been variations in the primary studies in how CVD was defined.[1]
- **Coronary heart disease**: was associated with 2 times higher odds of severe COVID-19[2] and 3.6 times higher odds of mortality.[3]
- **Hypertension**: was associated with 2.6 times higher odds of severe COVID-19 and 2.5 times higher odds of mortality.[1]
- **Diabetes mellitus**: was associated with 2.5 times higher odds of severe COVID-19 and 2.1 times higher odds of mortality.[1]
- **Renal disease**: was associated with 2.2 times higher odds of severe COVID-19 and 3.1 times higher odds of mortality.[1]
- **Cerebrovascular disease**: was associated with 2.8 times higher risk of severe COVID-19[2] and mortality[3]; however, it was not specified if stroke occurred prior to or following infection.
- **Liver disease:** was associated with 2.8 times higher odds of mortality,[4] but was not significantly associated with severe COVID-19.[5]
- **Smoking**: *current smoking* was associated with 1.8 times higher risk of severe COVID-19 compared to former smoking and never smoking, but not mortality, and any *smoking history* was associated with 1.3 times higher risk of severe COVID-19 and mortality compared to never smoking.[6]
- **Obesity**: was associated with 2.2 times higher odds of mortality,[3] but there was an absence of moderate or high-quality reviews to determine the association with severe COVID-19.
- **Any cardiovascular risk factor or cardiovascular co-morbidity** : significant predictor of COVID-19 case fatality rate.[7]
- **Cholesterol levels, arrhythmias, diet, physical activity, alcohol consumption and dementia**: Absence of moderate or high-quality quality reviews to determine associations between these factors and outcomes with COVID-19.
- **Incident cardiovascular complications following COVID-19**: Of those hospitalised with COVID-19, the following incident cardiovascular complications were identified: acute heart failure (2%),[7] myocardial infarction (4%),[7] myocardial injury (10%),[7] angina (10%)[7], arrhythmias (18%),[7] venous thromboembolism (25%),[8] pulmonary embolism (19%)[8] and deep vein thrombosis (7%).[8] Acute cardiac injury was associated with 17 times higher odds of mortality.[1] The impact of COVID-19 on long-term cardiovascular health was not investigated.

Background

Public Health England commissioned researchers at the Liverpool Centre for Cardiovascular Science, University of Liverpool to conduct an umbrella review investigating the associations between cardiovascular disease (CVD) and COVID-19. Findings will inform the ongoing evaluation of the NHS Health Check programme, which aims to prevent heart disease, stroke, diabetes, kidney disease, and some cases of dementia among adults aged 40-74 years. It does this through earlier awareness, assessment, and management of the major risks factors and conditions driving premature death, disability and health inequalities in England. Findings of this umbrella review will help commissioners and providers of the NHS Health Check programme consider the contribution that tackling CVD can make to mitigating against poor COVID-19 outcomes.

Aim and Research Questions

The aim of this umbrella review was to identify and examine associations between cardiovascular risk factors or CVD and COVID-19. The review addresses the following research questions:

1. What is the association between cardiovascular risk factors or CVD and health outcomes, hospitalisation, mechanical ventilation and mortality caused by COVID-19?
2. What is the impact of COVID-19 on cardiovascular health?

Methods

This umbrella review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] Although there was no published protocol, the research questions, search strategy, and inclusion/exclusion criteria were independently developed by Public Health England prior to the commencement of the review by the research team.

Inclusion criteria

In brief, systematic reviews or meta-analyses examining associations between cardiovascular risk factors, CVD or cerebrovascular disease and any health outcomes with COVID-19, were eligible for inclusion. Reviews which examined the impact of COVID-19 on cardiovascular health were also eligible for inclusion. Reviews which were focused on children (aged <18 years) were excluded. Only reviews published in English language were eligible for inclusion. Further details of the inclusion criteria are provided in Appendix 1.

Search strategy

The search was conducted in early November 2020, and the following electronic databases were searched from January 1, 2020 to November 5, 2020: Cochrane Library, Ovid Medline, Ovid Emcare, Embase, Epistemonikos COVID-19, EPPI Living Map, Evidence Aid, Global Health, LENUS, medRxiv, Norwegian Institute of Public Health, PROSPERO, PubMed and the World Health Organisation. Exploded Medical subject headings (MesH) terms were combined with appropriate free-text terms for CVD, cardiovascular risk factors and COVID-19. These were mapped across different databases. Where available, appropriate systematic review search filters were applied to the search to limit the number of results to this type of review. The search strategy conducted in Medline is shown in Appendix 2.

Study selection

The results from the different electronic databases were exported into EndNote X9 and duplicates were removed. Two reviewers (SLH and BJRB) completed title and abstract screening independently in duplicate. Of the potentially included reviews, full-texts were retrieved and

also independently screened in duplicate by the same two reviewers to identify reviews for inclusion. Disagreements were resolved through discussion to reach a consensus.

Data extraction

A data extraction form was pre-defined in Microsoft Excel with the following information: first author, review search dates, number of included studies, countries of included studies, study designs of included studies, number of patients, population inclusion criteria, exposures examined, outcomes examined, whether a meta-analysis was performed (yes/no), methods if meta-analysis was performed (e.g. random-effects or fixed-effects model), results for each exposure and outcome of interest (and number of studies and patients for each analysis if different from the total study sample), quality assessment results, conclusions and reported limitations. Two reviewers (SLH and BJRB) independently completed the data extraction in duplicate for ten of the reviews (12%) and achieved good agreement (≥80%). Data extraction for the remaining included reviews was completed by one reviewer (SLH or BJRB).

Quality assessment

Two reviewers (JMR-C and JZ) independently critically assessed the quality of ten included reviews (12%) using the AMSTAR 2, which is a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions.[10] The reviewers discussed any disagreement until optimal agreement was achieved (100%), and the quality assessment of the remaining included reviews was completed by one reviewer (JMR-C or JZ). The AMSTAR 2 includes 16 items, and as the AMSTAR 2 is designed for reviews of interventions, we modified the items which referred to “interventions” to refer to “exposures” in the included reviews. Using the AMSTAR 2 checklist, each included review was given an overall confidence

rating of “critically low” (more than one critical flaw with or without non-critical weaknesses), “low” (one critical flaw with or without non-critical weaknesses), “moderate” (more than one non-critical weakness) or “high” (no or one non-critical weakness).

Results

Screening

The searches resulted in 692 studies identified and after removal of duplicates, 492 studies were screened at the title and abstract stage (Figure 1). After reviewing the title and abstracts, 301 (61.2%) were removed, and the full-texts were retrieved for 191 studies and subsequently assessed for eligibility. At the full-text screening stage, 107 articles were excluded and the reasons are listed in the PRISMA flow diagram. Attempts were made to contact the authors of one of the included reviews for further information, but no response was received. After full-text screening, 84 systematic reviews or meta-analyses were included in this umbrella review.

Characteristics of the included reviews

The number of studies in the included reviews ranged from three[11] to 212.[12] The earliest search date of the included reviews was to February 25, 2020,[13] and the most recent search date was to September 14, 2020.[14] Of the 84 reviews, 21 reported that all of the included studies only included data from China.[5 15-34] The reviews included observational studies such as case reports, case series, cross-sectional studies and retrospective and prospective cohort studies. Of the total reviews, 64 addressed research question one,[1-6 11-15 18-25 27-74] and 27 reviews addressed research question two.[1 7 14 17 19 20 31 34 39 41 43-45 50 52 58 60 75-84] Appendix 3 summarises the characteristics and results of the included reviews, which were relevant to this umbrella review. It was noted that duplication of primary studies within the included reviews was extensive.

More recent reviews tended to include larger numbers of patients, greater numbers of cohort studies, and data from a wider variety of countries. Therefore, in this umbrella review, for each risk factor, we have highlighted the findings from the largest, most recent review which was assessed as moderate- or high-quality.

Assessment of the quality of the included reviews

Of the 84 included reviews, according to the AMSTAR 2 rating, 33% (n=28 reviews) were assessed as critically low quality;[14 22-25 27 28 30 32 33 35 39 45 47-49 55 57 58 62 66 70 72 73 80 82 85 86] 29% (n=24) were assessed as low quality,[12 13 15 18-21 26 34 36 40-44 51 53 54 61 67 75 76 79 83] 37% (n=31) were moderate quality,[1-5 7 8 11 16 17 29 31 37 38 46 50 52 56 59 60 63-65 68 69 71 74 77 78 81 84] and only one review, which reported associations between smoking and outcomes with COVID-19, was assessed as high quality.[6]

The AMSTAR 2 criteria which were often met by the included reviews were: 1) outlining the research questions and inclusion criteria including the elements of participants, intervention, comparator group and outcomes (PICO) (AMSTAR 2 criteria #1), 2) explaining the selection of study designs for inclusion (AMSTAR 2 criteria #3), 3) performing duplicate screening and duplicate data extraction (AMSTAR 2 criteria #5 and #6), and 4) declaring potential conflicts of interest and sources of funding (AMSTAR 2 criteria #16). Most of the reviews achieved "Partially Yes" in the following sections: assessing selection bias and confounding factors in the risk of bias assessment (AMSTAR 2 criteria #9), and providing sufficient explanation on the method prior to its conduction (AMSTAR 2 criteria #2), although limited studies reported clear plans to investigate causes of heterogeneity. Although most reviews mentioned publication bias or planned for its assessment (AMSTAR 2 criteria #15), some of the reviews did not perform assessment of this bias or report this bias either due to small sample size, or no explanation was provided.

The AMSTAR 2 criteria which were not reported in the majority of the reviews, were: 1) a list of excluded studies and justifications for exclusion (AMSTAR 2 criteria #7), and 2) reporting sources of funding for studies included in the review (AMSTAR 2 criteria #10). Further, AMSTAR 2 criteria which were often not fulfilled in the included reviews, were: justification of restrictions of the search, adjustment for confounding factors in meta-analyses, assessment on the impact of risk of bias for individual studies on the results of the meta-analysis, and sufficient discussion and interpretation of the results with impact of individual risk of bias. The AMSTAR 2 ratings are reported in Appendix 4.

Research question 1: What is the association between cardiovascular risk factors or CVD and outcomes caused by COVID-19?

Table 1 and figures 2 and 3 provide summaries of the main findings for this research question; focussing on the outcomes which were most consistently reported in the included reviews (mortality and severe COVID-19). Although definitions for severe COVID-19 varied between the reviews, definitions typically included a composite of key outcomes, such as respiratory distress (e.g. respiratory rate >30 per minute), low oxygen saturation (e.g. oxygen saturation at rest <93%), mechanical ventilation, intensive care unit (ICU) admission, and/or mortality. Appendix 3 details the definitions used for severe COVID-19 in each included review.

Cardiovascular disease and outcomes with COVID-19

Over 45% of the included reviews (n=38) examined associations between CVD and outcomes with COVID-19. Definitions for CVD varied, with four reviews combining cerebrovascular disease and CVD,[18 37 59 74] one review included any cardiac pathology with the exception of

hypertension,[40] one review included hypertension, CVD, arrhythmia and heart failure,[42] and the remaining reviews did not report a clear definition.

Of the 38 reviews, 24 included meta-analyses that reported a significant association between CVD and higher mortality with COVID-19 (pooled odds ratios [ORs] or risk ratios [RRs] (95% confidence intervals [CIs]) range from 1.32 (1.1-1.58) to 11.08 (2.59-47.32)).[1-4 13 19 25 37-44 46 49 51 53 60-63 74] Of the 24 reviews, ten were rated as moderate quality,[1-4 37 38 46 60 63 74] the largest of which (Luo *et al.,*) suggested CVD was associated with 2.65 times higher odds of mortality with COVID-19 (pooled OR 2.65 (1.86-3.78), n=30 studies, considerable heterogeneity (I^2=86%)).[1] Luo *et al*., examined a range of exposures but did not provide a clear definition for CVD and there may have been variations in the primary studies in how CVD was defined.

Nineteen reviews reported a significant association between CVD and a higher likelihood of severe COVID-19 (pooled ORs or RRs (95% CIs) range from 1.79 (1.50-2.13) to 5.19 (3.25-8.29)).[1 2 5 18 21 23 27 28 30 31 34 40 41 47 50 53 55 58 59] However, the definition of severe COVID-19 was inconsistent across the reviews. Of the 19 reviews, five were rated as moderate quality,[1 2 31 50 59] the largest of which (Luo *et al*.,) suggested CVD was associated with 3.86 times higher odds of severe COVID-19 (pooled OR 3.86 (2.70-5.52), n=29 studies, substantial heterogeneity (I^2=63%)).[1]

One review which completed meta-regression analyses suggested that the age of patients had no impact on the association between CVD and severe COVID-19, but as the proportion of female patients in the severe group increased, so did the OR for the association between CVD and severe COVID-19 (P=0.02).[40] This indicates that the association between CVD and severe COVID-19 may be more pronounced in female patients; however, the quality of the review was rated as low.

Only one review did not find an association between CVD and mortality, but all of the patients included in this review had diabetes mellitus, the sample size was relatively small, and the review was rated as critically low quality.[57] One review (rated as low quality) completed a meta-regression and did not find a significant association between chronic heart disease and severe COVID-19 or mortality with COVID-19. This may have been due to analysing cardiac failure separately which was significantly associated with higher mortality.[12]

Five reviews examined associations between coronary heart disease (CHD) and outcomes with COVID-19. Four reviews reported a significant association between CHD and higher odds of mortality (pooled ORs (95%CIs) range from 2.66 (1.60-4.43) to 3.78 (2.42-5.90)).[2 3 37 51] Three of these reviews were rated moderate quality,[2 3 37] and the largest review included 11 studies and suggested CHD was significantly associated with 3.63 times higher odds of mortality with COVID-19 (pooled OR 3.63 (1.52-8.65), considerable heterogeneity (I^2=100%)).[3] Two reviews reported a significant association between CHD and higher odds of severe COVID-19; [2 15] only one of these reviews was rated moderate quality and reported CHD was associated with 2 times higher odds of severe COVID-19 (pooled OR 2.03 (1.39-2.97), moderate heterogeneity (I^2=44%)).[2]

Cerebrovascular disease and outcomes with COVID-19

Of the 84 reviews, 24 examined associations between cerebrovascular disease and outcomes with COVID-19.[2-5 12 13 23 28 31 38 39 41-44 46 47 49 53 57 61 63 68 72] Of these, nine reviews were rated as moderate quality.[2-5 31 38 46 63 68] The most recent moderate quality review with the largest number of studies investigating associations with mortality reported cerebrovascular disease was associated with a significant 2.75 times higher risk of mortality (pooled RR 2.75 (1.54-4.89), n=11 studies, considerable heterogeneity (I^2=99%)).[3] The most recent moderate quality review with the largest number of studies examining the association between cerebrovascular disease and

severe COVID-19 reported that cerebrovascular disease was associated with 2.77 times higher risk of severe COVID-19 (pooled RR 2.77 (1.70-4.52), n=12 studies, moderate heterogeneity (I^2=40%)).[2]

One moderate quality review reported a significant association between cerebrovascular disease and higher risk of ICU admission with COVID-19 (pooled RR, 4.52 (2.48-8.25), n=3 studies, low heterogeneity (I^2=5%)).[2] In contrast, one other moderate quality review did not find a significant association between cerebrovascular disease and ICU admission with COVID-19 (pooled RR 1.9 (0.9-4.0), n=4 studies, considerable heterogeneity (I^2=92%)).[63]

One review examined the association between cerebrovascular disease and mortality with COVID-19 specifically for people with diabetes and found no significant association; however, the review was rated as critically low quality.[57] One moderate quality review did not find a significant association between cerebrovascular disease and ICU mortality, but this review only included two studies and 67 patients.[38]

It was unclear in the majority of the reviews if stroke occurred prior to or following a COVID-19 diagnosis. Reviews which have explicitly examined the incidence of acute cerebrovascular disease with COVID-19 are described in 'Research question 2: the impact of COVID-19 on cardiovascular health'.

One review specifically examined stroke phenotypes and other potential risk factors for mortality amongst 115 patients with stroke and COVID-19 from 30 studies.[85] The review did not find a significant difference between stroke phenotypes (ischaemic vs. non-ischaemic) and mortality with COVID-19, and of several cardiovascular risk factors examined, only smoking was associated with higher mortality for patients with stroke and COVID-19 (pooled OR 6.0, 95% CI: 1.1-33.9).[85] However, this review was rated as critically low quality.

Hypertension and outcomes with COVID-19

Over half of the included systematic reviews examined associations between hypertension and outcomes with COVID-19 (n=46),[1-5 12 13 15 18 21-23 25 27 28 30-32 34-39 41-53 55-63]. Of the reviews which examined hypertension, fifteen were rated as moderate quality.[1-5 31 37 38 46 50 52 56 59 60 63] All of the moderate quality reviews reported significant associations between hypertension and poorer outcomes with COVID-19. Of the moderate quality reviews, Luo *et al*., included the largest number of studies and suggested hypertension was associated with 2.5 times higher odds of mortality (pooled OR: 2.50, (2.02-3.11), n=58 studies, considerable heterogeneity (I^2=93%)).[3] Luo *et al*., also reported a significant association between hypertension and higher odds of severe COVID-19 (pooled OR 2.56 (2.12-3.11), n=55 studies, considerable heterogeneity (I^2=83%)). It was unclear if the patients with hypertension had controlled or uncontrolled hypertension.

One moderate quality review reported a significant association between hypertension and higher odds of a composite adverse outcome of mortality, mechanical ventilation or severe COVID-19 (pooled OR 3.15 (2.26-4.41), n=38 studies, moderate heterogeneity (I^2=40%)).[50] Two moderate quality reviews suggested hypertension was associated with a higher risk of ICU admission,[2 63] with the largest, more recent review reporting a pooled RR of 1.4 (1.1-1.7), n=9 studies, and substantial heterogeneity (I^2=53%).[63]

One review stratified the results of the association between hypertension and severe COVID-19 by age group and found this association remained statistically significant for patients aged <50 and ≥50 years, but this review was rated critically low quality.[32] One review did not find a significant association between hypertension and mortality with COVID-19, but only included patients with diabetes mellitus, and this review was rated as critically low quality (pooled OR 0.60 (0.12-3.11)).[57] Associations between antihypertensive medication use and outcomes with COVID-19 were not examined in this umbrella review.

Diabetes mellitus and outcomes with COVID-19

Over half of the included reviews also examined associations between diabetes and outcomes with COVID-19 (n=45).[1-5 12 13 15 18 21-25 27-31 34 36-39 41 43 44 46 47 49 50 52-57 59-66] Of the reviews which examined diabetes mellitus, 18 were rated as moderate quality.[1-5 29 31 37 38 46 50 52 56 59 60 63-65] All 18 moderate quality reviews reported significant associations between diabetes mellitus and higher odds or risk of poorer outcomes with COVID-19. Luo *et al*., conducted the largest moderate quality review and reported significant associations between diabetes and higher odds of mortality (pooled OR 2.09 (1.80-2.42), n=63 studies, considerable heterogeneity (I^2=81%)), and severe COVID-19 (pooled OR 2.54 (1.89-3.41), n=58 studies, considerable heterogeneity (I^2=89%)).[1] However, the review did not further clarify if the included studies included people with type 1 diabetes, type 2 diabetes or both.

One moderate quality review reported a significant association between diabetes mellitus and 2.34 times higher odds of a composite adverse outcome of mortality, mechanical ventilation or severe COVID-19 (pooled OR 2.34 (1.64–3.33), n=34 studies, substantial heterogeneity (I^2=80%)).[50] Two moderate quality reviews suggested diabetes was associated with higher risk of ICU admission,[2 63] and the largest, more recent review reported a pooled RR of 1.9 (1.4-2.6), n=12 studies, and considerable heterogeneity (I^2=90%)).[63] The association between diabetes and mortality with COVID-19 was stratified by age group in one moderate quality review of nine studies, and the association only remained statistically significant for patients aged <70 years (pooled OR 2.05 (1.44-2.94), moderate heterogeneity (I^2=32%)).[29]

Renal disease and outcomes with COVID-19

There were 21 reviews included which examined associations between renal disease and outcomes with COVID-19.[1-4 13 23 25 27 31 37 41-44 46 47 49 53 58 63 70] All reviews compared renal/kidney

disease/disorder or chronic kidney disease to no renal disease/disorder. No reviews examined the impact of different stages of renal disease on outcomes with COVID-19. Eight reviews were rated as moderate quality.[1-4 31 37 46 63] All of the moderate quality reviews reported significant associations between renal disease and higher odds or risk of mortality (largest moderate quality review: pooled OR 3.07 (2.43-3.88), n=35 studies, substantial heterogeneity (I^2=73%)),[1] and severe COVID-19 (largest moderate quality review: pooled OR 2.20 (1.26-3.85), n=28 studies, considerable heterogeneity (I^2=77%)).[1]

Liver disease and outcomes with COVID-19

Fourteen reviews examined associations between liver disease and outcomes with COVID-19.[3-5 27 28 31 39 41-44 46 47 63] Some of the reviews referred to 'chronic liver disease' whilst others only specified 'liver disease', and no distinctions were made for the severity of liver disease. Six of these reviews were rated as moderate quality. Four moderate quality reviews examined the association between liver disease and mortality with COVID-19.[3 4 46 63] Of these, two reviews did not report a significant association,[3 4] whereas two reviews reported a significant association between liver disease and higher odds or risk of mortality.[3 4] The reviews which reported a significant association between liver disease and higher mortality had a more recent search and included more studies.[3 4] Islam *et al*., was one of the larger studies and reported a significant association between liver disease and 2.81 times higher odds of mortality (pooled OR 2.81 (1.31-6.01), n=8 studies, no heterogeneity (I^2=0%)).[4] Two moderate quality reviews did not report a significant association between liver disease and severe COVID-19, but both of these reviews were relatively older (searches until April 2020).[5 31]

Obesity and outcomes with COVID-19

Six reviews were identified which examined associations between obesity or body mass index (BMI) and outcomes with COVID-19.[3 5 11 30 53 73] Three of the reviews were rated as moderate quality.[3 5 11] The largest moderate quality review reported a statistically significant association between obesity and mortality (pooled OR 2.18, (1.10-4.34), n=7 studies considerable heterogeneity (I^2=99%)).[3] This review did not further specify what measures the included studies used to define obesity.

One further moderate quality review also suggested obesity was associated with increased risk of in-hospital critical care with COVID-19, but a meta-analysis was not performed.[11] One moderate quality review including only four studies of 221 patients reported no statistically significant association between BMI and severe COVID-19.[5]

Dyslipidemia and outcomes with COVID-19

One low quality meta-analysis was identified which examined associations between dyslipidemia and outcomes with COVID-19.[53] The meta-analysis included four studies (n=11,273 patients) and reported a significant association between dyslipidemia and mortality (pooled OR 1.26 (1.06-1.50). No significant association was found between dyslipidemia and severe COVID-19, although this was based on four studies of only 559 patients (pooled OR 0.63 (0.22-1.83)).

Smoking and outcomes with COVID-19

Of the included reviews, 20 examined associations between smoking and outcomes with COVID-19.[3 5 6 12 20 25 30 33 34 38 39 41 44 49 53 58 59 67 69 71] There were differences in the comparisons made in the reviews which examined smoking (e.g. current/former smoker vs. never smoker and current smoking vs. not current smoking). One of the reviews which examined smoking and outcomes

with COVID-19 was rated high quality,[6] and six reviews were rated moderate quality.[3 5 38 59 69 71] The high quality review by Reddy *et al*., reported a statistically significant association between current smoking and 1.80 times higher risk of severe COVID-19 (pooled RR 1.80 (1.14-2.85), n=5 studies, considerable heterogeneity (I^2=76%)), but no significant association between current smoking and disease progression, ICU admission, mechanical ventilation or mortality.[6] In this review, severe COVID-19 was defined a priori and based on the COVID-19 diagnostic criteria issued by the Chinese National Health Commission (dyspnoea, with a respiratory rate ≥ 30 breaths/min, oxygen saturation ≤ 93% at rest, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2 ratio) ≤ 300) or other acceptable criteria included the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria for severe community-acquired pneumonia.

There were some inconsistencies between reviews, as two moderate quality reviews did not find a significant association between current smoking and severe COVID-19,[5 59] and two moderate quality reviews and the high-quality review did.[6 69 71] However, the two reviews which did not report a significant association were relatively older and included fewer studies. One moderate quality review which examined smoking had a more recent search date than the high-quality review, and also did not find a significant association between current smoking and mortality with COVID-19.[3]

In the same high-quality review, smoking history was defined as current, former, and/or unspecified smokers. In this review, smoking history vs. never smoking was associated with severe (pooled RR 1.31 (1.12-1.54), n=12 studies, low heterogeneity (I^2=12%)), disease progression (pooled RR 2.18 (1.06-4.49), n=5 studies, substantial heterogeneity (I^2=69%)), mechanical ventilation (pooled RR 1.20 (1.01-1.42), n=4 studies, no heterogeneity (I^2=0%)) and

mortality (pooled RR 1.26 (1.20-1.32), n=9 studies, no heterogeneity (I^2=0%)), but not ICU admission.[6]

Alcohol and outcomes with COVID-19

One moderate quality review was identified which examined associations between alcohol consumption and severe COVID-19.[5] The review only identified one study which included 30 patients with COVID-19 and did not find a statistically significant association between alcohol use and severe COVID-19 (OR 1.86 (0.40-8.69)).

Arrhythmias and outcomes with COVID-19

Four reviews examined the association between cardiac arrhythmias and outcomes with COVID-19, including mortality or severe COVID-19.[42 51 53 58] All four of these reviews were rated low or critically low quality. Three reviews examined the association between arrhythmias and mortality with COVID-19, and all reported a statistically significant association with higher odds of mortality (pooled ORs 2.13 (1.72-2.65), 2.75 (1.43-5.25) and 3.89 (2.51-6.02)).[42 51 53] Two reviews reported a statistically significant association between arrhythmias and higher odds of severe COVID-19 (pooled ORs 16.51 (6.69-40.77) and 14.8 (8.9-24.6)).[53 58] No reviews which examined associations between arrhythmias and outcomes with COVID-19 further described the types of arrhythmias experienced. Furthermore, it was unclear in the reviews if arrhythmia was present prior to COVID-19; however, reviews which have examined the incidence of arrhythmia with COVID-19 are described in 'Research question 2: the impact of COVID-19 on cardiovascular health'.

Multiple cardiovascular risk factors and outcomes with COVID-19

One moderate quality review examining 21 studies with >77,000 patients reported increasing numbers of cardiovascular co-morbidities or cardiovascular risk factors was significantly associated withCOVID-19 case fatality rate (regression coefficient 0.004, 95% CI: 0.003-0.005, p<0.001).[7]

Research question 2: What is the impact of COVID-19 on cardiovascular health?

Figure 4 provides a summary of the main findings for this research question. All of the reviews which examined the impact of COVID-19 on cardiovascular health were completed in the acute phase, and no reviews were found which examined the impact of COVID-19 on longer-term cardiovascular outcomes. Eight reviews reported the pooled incidence of acute cardiac injury in patients with COVID-19.[7 45 52 60 75-78] Of these reviews, only two further defined acute cardiac injury.[77 78] One of the reviews defined acute cardiac injury as "serum levels of troponin or CK-MB above the 99th percentile upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography",[77] and one review defined acute cardiac injury as "troponin levels >28 pg/ml".[78] Five of the reviews were rated as moderate quality,[7 52 60 77 78] and amongst these reviews the incidence of acute cardiac injury ranged from 6%[52] to 25%.[60] The largest moderate quality review included over 77,000 participants and suggested the incidence of acute myocardial injury was 10.3%.[7] This review also reported meta-regression analysis, with pre-existing cardiovascular comorbidities or risk factors as significant predictors of cardiovascular complications (P=0.019).

Twelve reviews examined the association between acute cardiac injury and outcomes with COVID-19.[1 19 20 31 41 43 44 50 58 60 76 79] Of these, four reviews were rated as moderate quality.[1 31 50 60] Two moderate quality reviews reported a significant association between acute cardiac injury

and higher odds of mortality.[1 60] The largest, most recent moderate quality review reported an association between acute cardiac injury and 17 times higher odds of mortality with COVID-19 (pooled OR 16.97 (7.87-36.57), n=14 studies, considerable heterogeneity (I^2=89%)).[1]

One moderate quality review reported a significant association between acute cardiac injury and a composite adverse outcome of mortality, mechanical ventilation or severe COVID-19 (pooled OR 10.58 (5.00-22.40), n=12 studies, substantial heterogeneity (I^2=59%)).[50] One moderate quality review reported a significant association between acute cardiac injury and severe COVID-19 (pooled OR 6.57 (3.70-11.65), n=11 studies, considerable heterogeneity (I^2=75%));[1] whereas, one moderate quality review did not find a significant association between acute cardiac injury and severe COVID-19, but this review was relatively older and included fewer studies.[31]

One moderate quality meta-analysis of 17 studies estimated the incidence of venous thromboembolism (VTE), pulmonary embolism, and deep vein thrombosis as 25% (95% CI: 19%-31%), 19% (13%-25%) and 7% (4%-10%), respectively for patients hospitalised with COVID-19. All of these estimates were shown to have considerable heterogeneity. A higher incidence of VTE was observed in severe compared to non-severe patients (pooled RR 4.76 (2.66-8.50), moderate heterogeneity (I^2=47%)).[8]

The incidence of new-onset arrhythmia developed during hospitalisation with COVID-19 was reported in three reviews[7 45 81]. Two of these reviews were rated moderate quality and the larger of these reported incidence of arrhythmias as 18.4% (95% CI: 7.8%-32.3%).[7] Two moderate quality reviews estimated the incidence of acute heart failure,[7 17] with the larger, most recent, review reporting an incidence of 2.0% (0.9%-3.4%).[17] The same review was also the only

moderate quality review to estimate the incidence of angina (10.2% (3.2%-20.5%)) and myocardial infarction (3.5% (2.1%-5.3%)) following COVID-19.[7]

The incidence of acute cerebrovascular disease with COVID-19 was reported in two reviews, with similar incidence estimates (1.4% (95% CI: 1.0%-1.9%)[80] and 2% (95% CI: 1-4%)).[14] However, these reviews were both rated as critically low. One of these reviews suggested hypertension, diabetes mellitus and coronary artery disease were significantly associated with higher odds of incident cerebrovascular disease following COVID-19.[14]

Two moderate quality reviews examined the incidence of any cardiovascular complication with COVID-19.[7 84] The most recent moderate quality review reported a pooled incidence of 14.1% (10.3%-20.2%) for any cardiovascular complication developed in-hospital with COVID-19.[7] The association between cardiovascular complications and mortality with COVID-19 was examined in two reviews.[7 39] One of these reviews was rated as moderate quality and reported a statistically significant association between cardiovascular complications and COVID-19 case fatality rate (regression coefficient 0.001, 95% CI: 0.000-0.003, P=0.038).[7]

One review examined post-mortem cardiac histopathologies and reported the results of 23 studies qualitatively.[82] The review concluded that the most reported pathology was myocardial hypertrophy (51%), followed by myocardial fibrosis (50%), coronary small vessel disease (26%), myocardial cell infiltrate (16%), cardiac amyloidosis (6%), and myocardial necrosis (5%).[82] However, this review was based on a relatively small sample (n=430 patients) and was rated as critically low quality.

Strengths and limitations

This umbrella review included a systematic search strategy to examine a wide-range of cardiovascular risk factors and cardiovascular conditions in relation to outcomes with COVID-19, and the impact of COVID-19 on cardiovascular health. Search terms for cardiovascular biomarkers were not included as this was beyond the scope of the current review, and the impact of treatments for COVID-19 on the observed associations were not examined. Furthermore, only reviews available in English language were included. The quality of the included reviews varied, many critically low- and low-quality reviews according to the AMSTAR 2 checklist were included and there was duplication of primary studies within the reviews. However, we have focused on the results of reviews which were rated as moderate and high-quality. Within the included reviews, there were inconsistencies in definitions used for severe COVID-19 and reporting of adjustment for confounding factors. Confounding factors such as age, sex and ethnicity may impact the results of reviews, but it was not clear in many of the reviews if the studies included in meta-analyses adjusted for these factors. Furthermore, as there was a wide range of study designs in the included studies, there was likely high variation in how the comorbidities and risk factors were established. Reviewing all of the primary studies to discern the extent of this is beyond the scope of the report. High levels of heterogeneity were often reported in meta-analyses, which was not usually further investigated. Twenty-one reviews also included data from China exclusively. Pre-prints were included because of the rapidly emerging evidence base, but the results reported in these articles may be subject to change following peer-review. Due to the nature of the research questions, only observational evidence was available to address the questions, which typically provides low certainty evidence and cannot infer causality.

Conclusions

In this umbrella review, 84 systematic reviews were identified which examined the association between cardiovascular disease or cardiovascular risk factors and outcomes with COVID-19, or determined the impact of COVID-19 on incident cardiovascular complications. Of these reviews, 31 were assessed as moderate quality and only one review was assessed as high-quality, which examined associations between smoking and outcomes with COVID-19. Duplication of included primary studies was noted within the reviews; therefore, findings were focused on the largest, most recent moderate or high-quality review identified for each risk factor and outcome investigated. Limitations of the reviews included high levels of heterogeneity which were not further investigated and lack of clarity regarding controlling for potential confounding factors.

Research question 1: What is the association between cardiovascular risk factors or CVD and outcomes caused by COVID-19?

CVD, hypertension, diabetes mellitus and renal disease were significantly associated with higher likelihood of severe COVID-19 and mortality with COVID-19. The only high-quality review identified reported current smoking was associated with higher risk of severe COVID-19, but not mortality, and smoking history was associated with higher risk of severe COVID-19 and mortality. Liver disease was associated with higher odds of mortality, but no significant association was observed between liver disease and severe COVID-19. Obesity and increasing number of cardiovascular co-morbidities were also associated with higher odds of mortality with COVID-19, but there was an absence of moderate or high-quality reviews to determine the association between obesity or increasing number of cardiovascular co-morbidities and severe COVID-19.

Although cerebrovascular disease was associated with higher likelihood of adverse outcomes with COVID-19, it was often unclear if stroke occurred prior to or following infection. Therefore, prospective studies are needed to further determine the association between COVID-19 and incident stroke. There was insufficient evidence to make conclusions regarding alcohol consumption and outcomes with COVID-19. Although an extensive search was conducted, no moderate quality reviews were identified which examined cholesterol levels, arrhythmias, diet, physical activity or dementia and outcomes with COVID-19**.** Furthermore, no reviews examined the impact of cardiovascular health on long-COVID, which is an ongoing symptom burden following COVID-19.

Research question 2: What is the impact of COVID-19 on cardiovascular health?

In the largest moderate quality review identified, incident acute cardiac injury with COVID-19 was 10%, incidence of arrhythmias was 18%, and incidence of venous thromboembolism, pulmonary embolism and deep vein thrombosis was 25%, 19% and 7%, respectively. All included reviews examined in-hospital cardiovascular outcomes only and the impact of COVID-19 on long-term cardiovascular health was not investigated.

Implications for practice

Identifying cardiovascular risk factors for worsened COVID-19 prognosis is important to identify high-risk patient groups and for targeting of intervention strategies. Many of the risk factors identified as significantly associated with adverse outcomes with COVID-19 are potentially modifiable. Therefore, primary and secondary prevention strategies which target these cardiovascular risk factors and conditions may improve outcomes for people following COVID-19. Large-scale cardiovascular prevention programmes such as the NHS Health Check aim to help adults lower their risk of developing cardiovascular and cardiovascular-related conditions.

Given the association between CVD, cardiovascular risk factors, and adverse outcomes with COVID-19 shown in this umbrella review, utilisation of such programmes might help adults reduce their risk of adverse outcomes with COVID-19. Further research should focus on the impact of multiple cardiovascular risk factors and associations with COVID-19, as cardiovascular risk factors rarely occur in isolation.

Table 1. Summary of evidence for associations between cardiovascular disease or cardiovascular risk factors and severe COVID-19 or mortality with COVID-19.

Exposure	**# reviews**	**# moderate or high-quality reviews***	**Consistent associations reported across moderate or high-quality reviews?**	**Largest moderate or high-quality reviews and reported findings**
CVD	38	13 moderate	Yes	Luo *et al*.,[1] Pooled OR for mortality: 2.65 (95% CI: 1.86-3.78), n=30 studies, I^2=86% Pooled OR for severe COVID-19: 3.86 (95% CI: 2.70-5.52), n=29 studies, I^2=63%
Cerebrovascular disease‡	24	9 moderate	Yes	Noor *et al*.,[3] Pooled RR for mortality: 2.75 (95% CI: 1.54-4.89), n=11 studies, I^2=99% Fang *et al*.,[2] Pooled RR for severe COVID-19 2.77 (95% CI: 1.70-4.52), n=12 studies, I^2=40%
Hypertension	46	15 moderate	Yes	Luo *et al*.,[1] Pooled OR for mortality: 2.50 (95% CI: 2.02-3.11), n=58 studies, I^2=93% Pooled OR for severe COVID-19: 2.56 (95% CI: 2.12-3.11), n=55 studies, I^2=83%
Diabetes mellitus	45	18 moderate	Yes	Luo *et al*.,[1] Pooled OR for mortality: 2.09 (95% CI: 1.80-2.42), n=63 studies, I^2=81% Pooled OR for severe COVID-19: 2.54 (95% CI: 1.89-3.41), n=58 studies, I^2=89%
Renal disease	21	8 moderate	Yes	Luo *et al*.,[1] Pooled OR for mortality: 3.07 (95% CI: 2.43-3.88), n=35 studies, I^2=73% Pooled OR for severe COVID-19: 2.20 (95% CI: 1.26-3.85), n=28 studies, I^2=77%
Liver disease	14	6 moderate	No: 2 reviews found a significant association between liver disease and mortality and 2 did not	Islam *et al*.,[4] Pooled OR for mortality: 2.81 (95% CI: 1.31-6.01), n=8 studies, I^2=0% Wu, Liu *et al*.,[5] Pooled OR for severe COVID-19: 0.81 (95% CI: 0.47-1.40), n=11 studies, I^2 NR
Smoking	20	1 high 6 moderate	No: 2 moderate quality reviews did not find a significant association between current smoking and severe COVID-19, and 2 moderate quality reviews and 1 high-quality review did	Reddy *et al*.,[6] (high quality) Current smoking vs. not current smoking Pooled RR for mortality: 1.46 (95% CI: 0.83-2.60), n=7 studies, I^2=81% Pooled RR for severe COVID-19: 1.80 (95% CI: 1.14-2.85), n=5 studies, I^2=76% Smoking history vs. never smoking Pooled RR for mortality: 1.26 (95% CI: 1.20-1.32), n=9 studies, I^2=0%

				Pooled RR for severe COVID-19: 1.31 (95% CI: 1.12-1.54), n=12 studies, I^2=12%
Obesity	6	3 moderate	No: 2 reviews reported a significant association between obesity and worse outcomes with COVID-19 and 1 review did not	Noor *et al*.,[3] Pooled OR for mortality: 2.18 (95% CI: 1.10-4.34), n=7 studies, I^2=99%
Dyslipidemia	1	0	N/a	N/a
Arrhythmias	4	0	N/a	N/a
Diet	0	0	N/a	N/a
Physical activity	0	0	N/a	N/a
Dementia	0	0	N/a	N/a

*Rated using the AMSTAR 2 criteria

‡unclear if cerebrovascular disease occurred prior to or following infection with COVID-19

CI: confidence interval; NR: not reported; OR: odds ratio; RR: risk ratio.

Figure 1. PRISMA flow diagram.

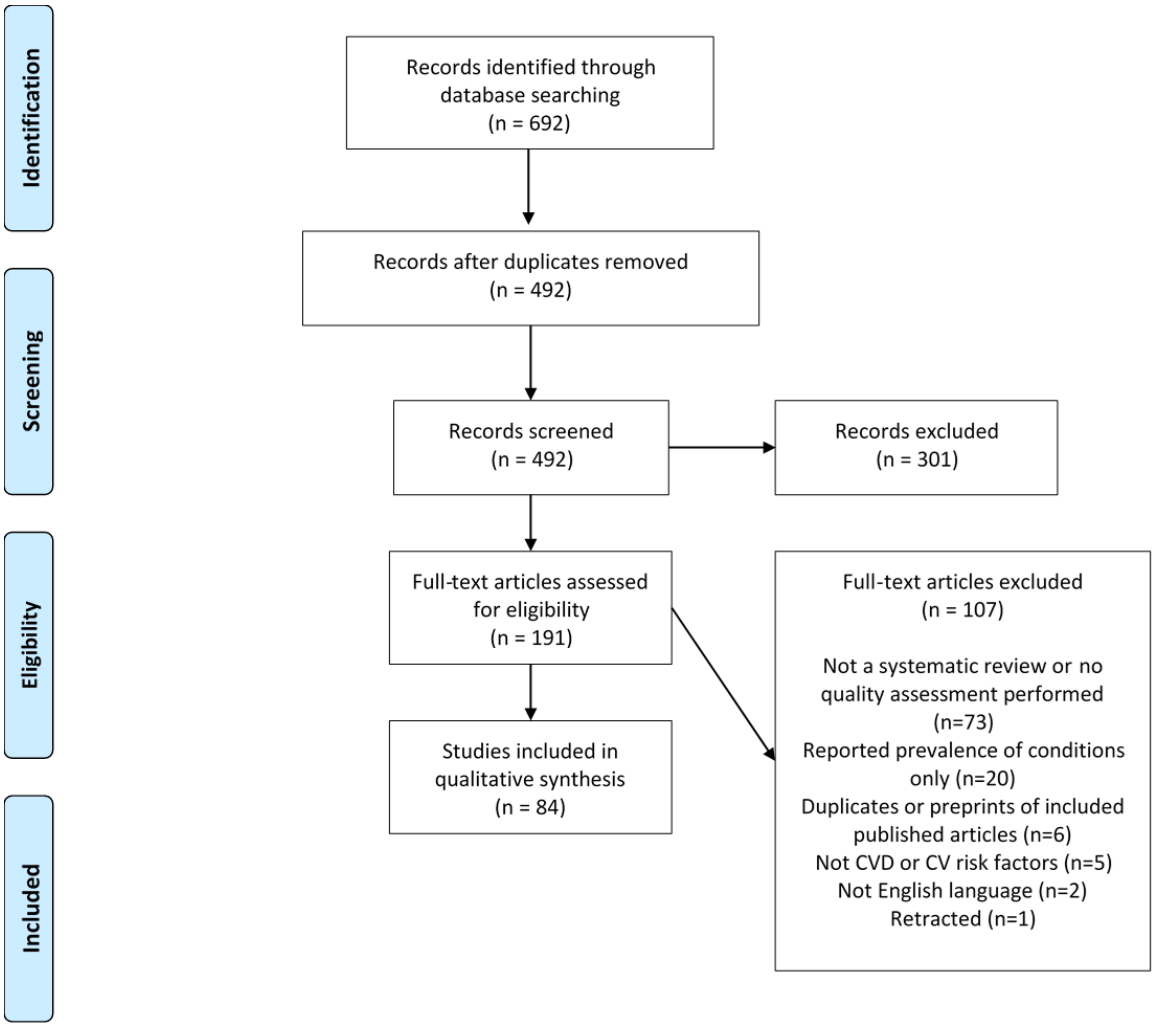
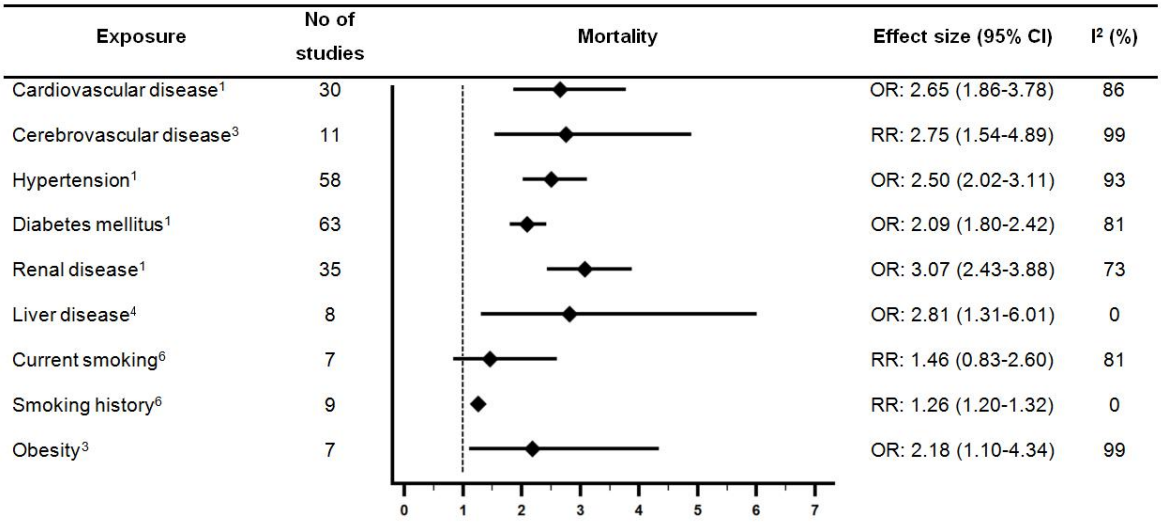
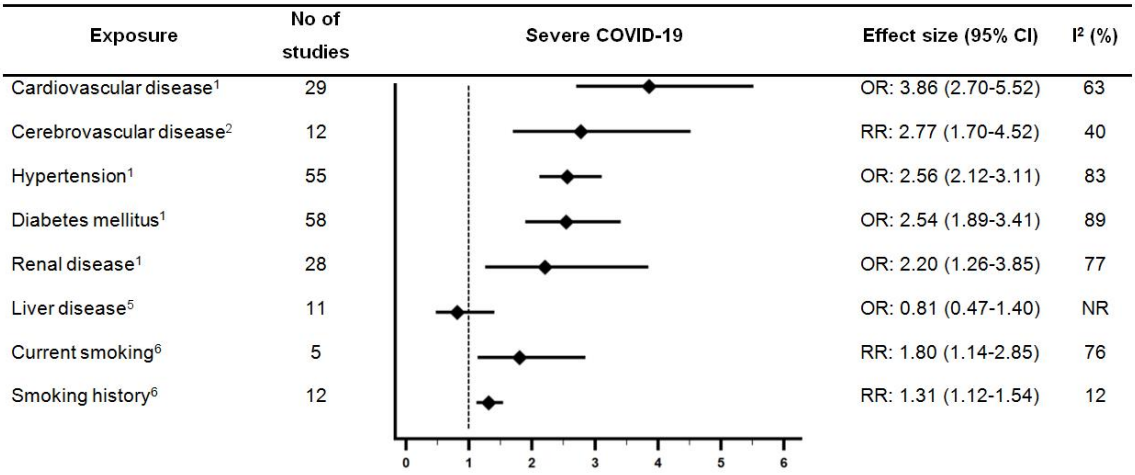


Figure 2. Forest plot showing results of meta-analyses from moderate or high-quality reviews which investigated associations between cardiovascular disease or cardiovascular risk factors and mortality with COVID-19.



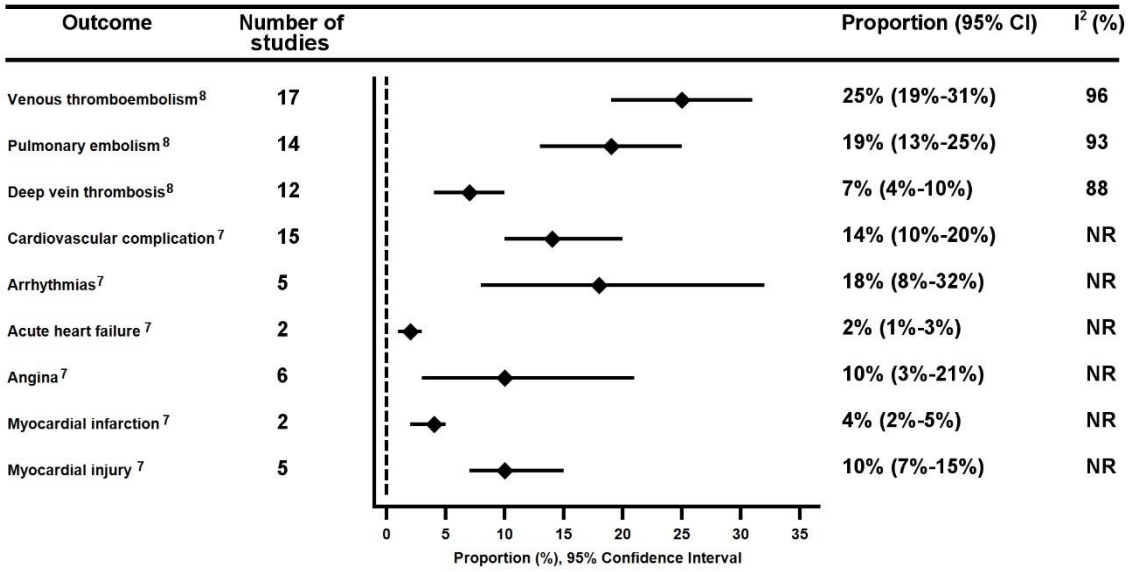
Largest moderate- or high-quality review included, according to assessment with the AMSTAR 2 criteria. No moderate or high-quality reviews with meta-analyses were identified which examined dyslipidemia, alcohol or arrhythmias and mortality with COVID-19. CI: confidence interval; OR: odds ratio; RR: relative risk.

Figure 3. Forest plot showing results of meta-analyses from moderate or high-quality reviews which investigated associations between cardiovascular disease or cardiovascular risk factors and severe COVID-19.



Largest moderate- or high-quality review included, according to assessment with the AMSTAR 2 criteria. CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk. No moderate or high-quality reviews with meta-analyses were identified which examined dyslipidemia, alcohol or arrhythmias and severe COVID-19.

Figure 4. Forest plot showing results of meta-analyses from moderate or high-quality reviews which investigated incident cardiovascular complications following hospitalisation with COVID-19.



Largest moderate- or high-quality review included, according to assessment with the AMSTAR 2 criteria. CI: confidence interval; NR: not reported.

Appendix 1. Inclusion criteria.

Systematic reviews or meta-analyses were eligible for inclusion if the reviews examined associations between cardiovascular risk factors, CVD or cerebrovascular disease and any health outcomes with COVID-19, including but not limited to hospitalisation, ventilation and mortality. Systematic reviews assessing any of the following cardiovascular risk factors and outcomes with COVID-19 were eligible for inclusion: smoking, hypertension, obesity, sedentary behaviour/physical inactivity, alcohol use, diet, cholesterol, familial hypercholesterolaemia, hyperlipoproteinemia type II, hyperglycaemia, prediabetic state, diabetes, atrial fibrillation, renal insufficiency, kidney diseases, liver diseases, fibrosis, and dementia. Reviews were also eligible for inclusion if the reviews examined the impact of COVID-19 on cardiovascular health i.e. incident cardiovascular or cerebrovascular events. Studies which reported previous cardiovascular history for patients with COVID-19, but did not examine associations with outcomes were excluded. In accordance with the Database of Abstracts of Reviews of Effects (DARE) criteria, to be included, the reviews needed to have detailed the inclusion and exclusion criteria, conducted an adequate search, assessed the quality of included studies, synthesised the results of the included studies and provided sufficient details of the characteristics of the included studies.[87] Pre-prints, grey literature or peer-reviewed publications were eligible for inclusion. Where a pre-print and a peer-reviewed publication of the same systematic review was found, only the peer-reviewed publication was included. Reviews which were focused on children (aged <18 years) were excluded. Only reviews published in English language were eligible for inclusion.

Appendix 2. Medline Search Strategy.

#	Searches
1	exp Comorbidity/
2	comorbidit*.tw.
3	exp Cardiovascular Diseases/
4	exp Cardiology/
5	(((heart or cardiovascular) adj (disease* or illness* or anomal* or infection* or abnormalit*)) or CVD or cardio* or cardiac*).tw.
6	1 or 2 or 3 or 4 or 5
7	exp Coronavirus/
8	exp Coronavirus Infections/
9	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw.
10	(coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus*).tw.
11	(Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019").tw.
12	(COVID-19 or COVID19).tw.
13	(SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARS-CoV2 or SARSCov19 or SARS-Cov19 or SARSCov-19 or SARS-Cov-19).tw.
14	(((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw.
15	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).tw.
16	"severe acute respiratory syndrome*".tw.
17	("long covid" or "long covid-19" or "long covid19" or "long coronav*" or "post acute covid" or "post acute coronav*").tw.
18	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	exp Smoking/
20	smoking.tw.
21	exp Hypertension/
22	hypertens*.tw.
23	"high blood pressure".tw.
24	exp Obesity/
25	obes*.tw.
26	exp Sedentary Behavior/
27	("sedentary behavio?r*" or "physical inactiv*").tw.
28	exp Alcohol-Induced Disorders/
29	alcohol.tw.
30	exp Diet/
31	diet*.tw.
32	exp Cholesterol/
33	cholesterol.tw.
34	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	exp Atrial Fibrillation/
36	"atrial fibrillation".tw.
37	exp Hyperlipoproteinemia Type II/
38	hyperlipoproteinemia*.tw.
39	"familial hypercholesterolemia".tw.
40	exp Dementia/

41	dementia.tw.
42	exp Hyperglycemia/
43	hyperglycemia.tw.
44	exp Prediabetic State/
45	("prediabetic state" or "pre diabetic state" or "pre diabet*").tw.
46	exp Renal Insufficiency/
47	exp Kidney Diseases/
48	((kidney or renal) adj diseas*).tw.
49	exp Liver Diseases/
50	liver disease*.tw.
51	exp Fibrosis/
52	fibrosis.tw.
53	cirrhosis*.tw.
54	exp Stroke/
55	stroke*.tw.
56	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57	(((comprehensive* or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or "cochrane database of systematic reviews".jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.
58	exp "Systematic Review"/
59	57 or 58
60	6 and 18 and 34 and 56 and 59
61	limit 60 to (english language and humans and yr="2020 - 2021")

Appendix 3. Characteristics and results of all included reviews.

Study characteristics	Exposures examined	Outcomes examined	Systematic review/ meta-analysis results
First and second author surname Search dates N=studies (n=patients) Primary study countries Study designs of included primary studies Quality assessment of primary studies AMSTAR2 grade	COVID-19 patients and cardiovascular condition(s) reported in primary data		Results of meta-analyses are presented unless otherwise stated, such as narrative review findings from a systematic review without meta-analysis.
Aggarwal, Cheruiyot[40] November 1, 2019 to April 20, 2020 N=18 studies (4,858 patients) 16 China, 2 US Case-control/cohort Newcastle-Ottawa Scale, range 6-9 AMSTAR2: Low quality	CVD defined as any cardiac pathology with the exception of hypertension	Severe COVID* Mortality Mortality in severe disease *Composite outcome of (1) Respiratory distress, respiratory rate ≥30 per minute; (2) Oxygen saturation at rest ≤93%; (3) Partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤300 mmhg; (4) Patients requiring mechanical ventilation/vital life support/intensive care unit admission; (5) Death.	OR (95% CI) CVD and Severe COVID 3.14 (2.32-4.24) I^2=0% CVD and mortality 11.08 (2.59-47.32) I^2=55% CVD and mortality in severe disease 1.72 (0.97-3.06) I^2=0% Meta-regression of odds of severe disease with CVD: The age of patients in the severe group had no significant influence (P=0.34). As the percentage of women in the severe group increased, so did the odds ratio of severe disease and CVD association (P=0.02).
Almeshari, Alobaidi[79] December 1, 2019 to April 23, 2020 N=16 studies; 2 cardiac injury (9,988 patients; 603 cardiac injury) 12 China, 3 USA, 1 Italy Case-control/Cohort NIH quality assessment tool: Good quality AMSTAR2: Low quality	Cardiac injury	Mechanical ventilation Mortality	Systematic review findings: One study demonstrated 25% patients required mechanical ventilation (n=52). In one study, 60% of patients with elevated Troponin required mechanical ventilation compared to 10% with normal Troponin. In one study (n=416), patients with cardiac injury 22% (18/82) required mechanical ventilation compared to 4.2% in those without cardiac injury (14/334).

Alqahtani, Oyelade[67] Inception to March 24, 2020 N=15 studies; 8 smoking (2,473 patients; 221 smoking studies) 14 China, 1 USA Case-control/cohort, case-series, Modified Newcastle-Ottawa Scale, range: 0.4 to 2.7 (9 studies >2, indicating low risk of bias) AMSTAR2: Low quality	Current/ex-smoker	Severe COVID (those who were admitted to ICU, had severe, oxygenation, needed mechanical ventilation or death)	RR (95% CI) Current smoking vs ex/never smoked 1.45 (1.03–2.04) I^2=92%
Bajgain, Badal[35] Inception to May 15, 2020. N=27 studies (22,753 patients) 18 China, 2 South Korea, 2 Italy, 2 USA, 1 Mexico, 1 UK, 1 Iran Study design NR Newcastle-Ottawa Scale, range 6-10 AMSTAR2: Critically low quality	Hypertension	Mortality	OR (95% CI) Hypertension 1.65 (1.01-1.85)
Barrera, Shekhar[36] December 1, 2019 to April 6, 2020 N=65 studies (15,794 patients) 46 China, 5 USA, 3 Singapore, 2 Italy, 2 Republic of Korea, 2 Hong Kong, 1 Australia, 1 Bolivia, 1 France, 1 Iran, 1 Japan Case-control/cohort, case-series GRADE, 18 low risk of bias, 3 some concerns, 44 high	Hypertension Diabetes mellitus Hypertension and diabetes mellitus	Severe COVID* Mortality ICU admission *ICU admission or mortality	RR (95% CI) Diabetes and severe COVID N=6 studies (1,991 patients) 1.50 (0.90-2.50) I^2=74% Diabetes and ICU admission N=3 studies (8,890 patients) 1.96 (1.19-3.22) I^2=80% Diabetes and mortality N=4 studies (2,058 patients) 2.78 (1.39-5.58) I^2=75% Hypertension and severe COVID N=8 studies (2,023 patients) 1.48 (0.99-2.23) I^2=69%

risk of bias. Overall confidence was low. AMSTAR2: Low quality			Hypertension and ICU admission N=4 studies (1,737 patients) 2.95 (2.18-3.99) I^2=0% Hypertension and mortality N=8 studies (3,107 patients) 2.39 (1.54-3.73) I^2=66%
Bennett, Tafuro[75] January 1, 2019 to April 26, 2020 N=45 studies (14,358 patients) 42 China, 2 USA, 1 Europe Case-control/cohort, cross-sectional Newcastle-Ottawa Scale, range 4-6 (out of 7) AMSTAR2: Low quality	COVID-19	Acute cardiac injury	Prevalence of acute cardiac injury N studies=4 (1,096 patients) 16.2%
Bhatia, Pedapati[85] Inception to May 22, 2020 N=30 studies (115 patients) Primary study origin NR Case-reports, case-series, case-control/cohort Oxford Centre for Evidence-based Medicine's Levels of Evidence and Grades of Recommendation "The risk of bias was not assessed systematically but was likely to be high in all studies since most were case reports, case series, and retrospective observational studies." AMSTAR2: Critically low quality	For stroke patients: Type of stroke Hypertension Diabetes Smoking Dyslipidaemia CAD	Mortality	OR (95% CI) Ischaemic vs. Non-ischaemic stroke N=73 patients 1.1 (0.3-4.1) NIH stroke scale (NIHSS) N=13 patients 1 (0.9-1.2) TOAST criteria N=52 patients Large artery disease 0.5 (0.1-2.3) Small vessel disease 0.16 (0.01-1.9) Cardioembolic 1.3 (0.3-4.7) Cryptogenic 1.5 (0.3-7.6) Hypertension N=72 patients 1.5 (0.6-3.9) Diabetes N=72 patients 2.1 (0.7-6.3)

			Old stroke N=72 patients 2.3 (0.2-2.7) Smoking N=47 patients 6 (1.1-33.9) Atrial fibrillation N=72 patients 1.1 (0.3-4.9) Dyslipidaemia N=65 patients 3 (0.96-9.7) CAD N=72 patients 6.4 (0.7-58)
Biswas, Rahaman[37] Inception to March 25, 2020 N=21 studies (47,807 patients) 19 China, 1 South Korea, 1 Singapore Case-control/cohort, RCT Newcastle-Ottawa Scale, range 5-8 AMSTAR2: Moderate quality	Hypertension Diabetes mellitus Cardio-cerebrovascular disease Renal disease CHD	Mortality	RR (95% CI) Hypertension N=4 studies (44,975 patients) 2.63 (2.32–2.98) I^2=0% Diabetes mellitus N=5 studies (44,995 patients) 3.34 (2.79–4.0) I^2=0% Cardio-cerebrovascular disease N=3 studies (44,701 patients) 5.06 (4.13–6.20) I^2=0% Renal disease N=3 studies (1,189 patients) 3.59 (1.49–8.67) I^2=0% CHD N=4 studies (1,346 patients) 3.84 (1.64–8.99) I^2=54%
Chang, Elhusseiny[38] Inception to May 1, 2020 N=28 studies (12,437 patients) 13 China, 9 USA, 2 UK, 1 Mexico, 1 Italy, 1 Spain, 1 France Case-control/cohort	Hypertension Diabetes mellitus CVD Smoking Cerebrovascular disease	ICU Mortality	OR (95% CI) Hypertension N=6 studies (1,327 patients) 2.02 (1.37-2.98) I^2=52% Diabetes mellitus N=5 studies (677 patients) 1.78 (1.19-2.65) I^2=42%

NIH quality assessment tool, 15 Good, 13 Fair AMSTAR2: Moderate quality			CVD N=6 studies (858 patients) 2.77 (1.76-4.37) I^2=45% Smoking N=3 studies (318 patients) 1.19 (0.48-2.92) I^2=42% Cerebrovascular diseases N=2 studies (67 patients) 3.84 (0.48-30.89) I^2=17%
Chen, Gong[15] Inception to March 6, 2020 N=9 studies (1,936 patients) 9 China Case-control/cohort Newcastle-Ottawa Scale, range 6-7 AMSTAR2: Low quality	Hypertension Diabetes mellitus CHD	Severe COVID (severe vs. Non-severe; or intensive care unit (ICU) vs. Non-ICU; or progression and improvement/ stabilization)	OR (95% CI) Hypertension N=9 studies (1,936 patients) 2.30 (1.76-3.00) I^2=50% Diabetes mellitus N=9 studies (1,936 patients) 2.67 (1.91-3.74) I^2=42% CHD N=6 studies (1,720 patients) 2.85 (1.68-4.84) I^2=0%
Chidambaram, Tun[41] Inception to May 7, 2020 N=109 studies (20,296 patients in the comparison of died and survived, 17,992 in the comparison of severe and non-severe) Comparison of died and survived: 32 China, 6 USA, 2 Spain, 1 UK, 1 Italy 1 Iran, 1 International Comparison of severe vs. Non-severe: 71 China, 1 Italy Case-control/cohort, cross-sectional, case-series Newcastle-Ottawa Scale, range 4-9 (1 scored 9, 54 scored 8, 39 scored 7, 6 scored 6, 6 scored 5, 3 scored 4) AMSTAR2: Low quality	Ever smoker Diabetes mellitus Hypertension CVD Heart failure Cerebrovascular disease Renal disease Chronic liver disease Acute cardiac injury Acute cardiac failure	Mortality Severe COVID* *Respiratory rate ≥30 breaths/minute, oxygen saturation ≤93% at rest, arterial oxygen tension (pao2) over inspiratory oxygen fraction (fio2) ratio ≤300 mm Hg or patients with >50% lesions progression within 24 to 48 hours in pulmonary imaging' or having 'evidence of respiratory failure and/or a need for mechanical ventilation, or shock or organ failure that requires intensive care monitoring.	OR (95% CI) Ever smoked Mortality: N=7 studies (10,419 patients) 1.43 (1.09-1.87) I^2=0% Severe COVID: N=10 studies (4,511 patients) 1.51 (1.06-2.14) I^2=62% Diabetes mellitus Mortality: N=27 studies (16,263 patients) 1.59 (1.41-1.78) I^2=23% Severe COVID: N=36 studies (7,552 patients) 2.09 (1.66-2.64) I^2=40% Hypertension Mortality: N=26 studies (15,947 patients) 1.90 (1.69-2.15) I^2=28% Severe COVID: N=33 studies (7,002 patients) 2.63 (2.08-3.33) I^2=64% CVD

			Mortality: N=25 studies (16,576 patients) 2.27 (1.88-2.79) I^2=71% Severe COVID: N=31 studies (6,932 patients) 2.83 (2.21-3.63) I^2=23% Heart failure Mortality: N=5 studies (9,910 patients) 2.08 (1.54-2.80) I^2=0% Severe COVID: N=3 studies (558 patients) 4.76 (1.34-17.0) I^2=0% Cerebrovascular disease Mortality: N=15 studies (2,437 patients) 2.63 (1.97-3.51) I^2=75% Severe COVID: N=13 studies (4,246 patients) 2.62 (1.76-3.90) I^2=7% Renal disease Mortality: N=15 studies (6,556 patients) 2.24 (1.78-2.81) I^2=20% Severe COVID: N=14 studies (4,442 patients) 2.62 (1.46-4.71) I^2=27% Chronic liver disease Mortality: N=6 studies (3,672 patients) 2.18 (1.40-3.40) I^2=20% Severe COVID: N=17 studies (8,869 patients) 1.56 (1.12-2.17) I^2=0% Acute cardiac injury Mortality: N=14 studies (2,860 patients) 5.42 (3.79-7.77) I^2=86% Severe COVID: N=3 studies (495 patients) 3.10 (2.55-3.77) I^2=0%
De Lorenzo, Kasal[16] February 4, 2020 OR April 2, 2020	COVID-19	Prevalence of acute cardiac injury in hospitalised patients	Proportion (95%CI) Acute cardiac injury N=8 studies (1,229 patients) 0.16 (0.09-0.27) I^2=92%

N=8 studies (1,229 patients) 8 China Case-control/cohort, case-series Newcastle-Ottawa Scale, 1 Good, 7 Fair AMSTAR2: Moderate quality			
Fang, Li[2] April 5, 2020 N=69 studies (15,071 patients) 67 China, 1 Japan, 1 Singapore Case-control/cohort Newcastle-Ottawa Scale, range 5-7 AMSTAR2: Moderate quality	Comorbidity Hypertension Diabetes mellitus CVD CHD Cerebrovascular disease Renal disease	Severe COVID* Mortality Admission to ICU *a. Respiratory distress, respiratory rate ≥ 30/min; b. Oxygen saturation of finger ≤ 93% in resting condition; c. Arterial partial pressure of oxygen (pao2) /oxygen concentration (fio2) ≤ 300 mmhg (1 mmhg = 0.133 kpa); including critical patients a. Respiratory failure requiring mechanical ventilation; b. Shock; c. Concomitant failure of other organs and requirement for ICU.	RR (95% CI) Comorbidity Severe COVID: N=16 studies 1.72 (1.44-2.06) I^2=83% Mortality: N=8 studies 1.68 (1.32-2.12) I^2=89% ICU: N=5 studies 1.82 (1.44-2.29) I^2=61% Hypertension Severe COVID: N=23 studies 2.09 (1.73-2.52) I^2=75% Mortality: N=11 studies 1.74 (1.31-2.30) I^2=84% ICU: N=5 studies 2.31 (1.99-2.69) I^2=0% Diabetes mellitus Severe COVID: N=23 studies 1.94 (1.6-2.36) I^2=43% Mortality: N=10 studies 1.75 (1.27-2.41) I^2=67% ICU: N=5 studies 1.88 (1.10-3.23) I^2=51% CVD Severe COVID: N=18 studies 2.74 (2.03-3.70) I^2=46% Mortality: N=11 studies 2.66 (1.60-4.43) I^2=76% ICU: N=5 studies 2.83 (1.98-4.05) I^2=0% CHD Severe COVID: N=8 studies 2.03 (1.39-2.97) I^2=44% Mortality: N=5 studies 3.16 (1.45-6.91) I^2=88% ICU: NR

			Cerebrovascular disease Severe COVID: N=12 studies 2.77 (1.70-4.52) I^2=40% Mortality: N=6 studies 4.55 (2.60-7.94) I^2=0% ICU: N=3 studies 4.52 (2.48-8.25) I^2=5% Renal disease Severe COVID: N=15 studies 2.38 (1.43-3.97) I^2=26% Mortality: N=5 studies 7.45 (3.5-15.86) I^2=0% ICU: N=2 studies 1.50 (0.37-5.99) I^2=0%
Figliozzi, Masci[50] April 24, 2020 N=49 studies (20,211 patients) Primary study origin NR Case-control/cohort, cross-sectional Newcastle-Ottawa Scale, range 7-8 AMSTAR2: Moderate quality	Diabetes mellitus Hypertension CVD Acute cardiac injury	Composite adverse outcome (mortality, mechanical ventilation, and severe COVID-19)	OR (95% CI) Diabetes mellitus N=34 studies (15,953 patients) 2.34 (1.64–3.33) I^2=80% Hypertension N=35 studies (9,360 patients) 2.25 (1.80–2.82) I^2=50% CVD N=19 studies (12,717 patients) 3.15 (2.26–4.41) I^2=40% Acute cardiac injury N=12 studies (2,069 patients) 10.58 (5.00–22.40) I^2=59%
Flook, Jackson[86] November 1, 2019 to April 29, 2020 N=33 studies (153,003 patients) 29 China, 1 France, 1 Italy, 1 Singapore, 1 UK Case-control/cohort The quality of included studies was assessed using an adapted checklist. Included studies were generally too small to detect a 10% increase in risk of disease, disease severity, or mortality. 3	Comorbidity	Mortality	Five (out of 33) studies presented evidence for the presence of any comorbidity being a risk factor for mortality in patients with COVID-19. No studies demonstrated evidence against.

were well power, 26 were descriptive or presented univariable analysis only. AMSTAR2: Critically low quality			
Florez-Perdomo, Serrato-Vargas[68] Inception to May 2020 N=7 studies (3,244 patients) 6 China, 1 Italy Case-control/cohort Newcastle-Ottawa Scale, range 5-6 AMSTAR2: Moderate quality	Cerebrovascular disease	Mortality	OR (95% CI) Cerebrovascular disease N=7 studies (3,244 patients) 2.78 (1.42-5.46) I^2=49%
Fridman, Bullrich[80] November 1, 2019 to May 29, 2020 N=10 studies (8,628 patients) Primary data origin NR Case-control/cohort, case-series, reports ROBINS-I tool, overall risk of bias was moderate. AMSTAR2: Critically low quality	COVID-19	Prevalence of new-onset stroke following COVID-19 diagnosis	Proportion (95% CI) Any stroke N=9 studies (3,306 patients) 0.02 (0.01-0.04) I^2=84% Ischemic stroke N=9 studies (5,322 patients) 0.02 (0.01-0.03) I^2=82%
Fu, Wang[17] Inception to March 2, 2020 N=43 studies (3,600 patients) 43 China Case-control/cohort, case-series NIH quality assessment tool, range 2-7 (9 low risk, 30 moderate, 4 high risk)	COVID-19	Cardiac failure	Prevalence % (95% CI) Cardiac failure N=4 studies (245 patients) 6.5 (2.2-12.2) I^2=78%

AMSTAR2: Moderate quality			
Gu, Zhang[77] April 24, 2020 N=53 studies (7,679 patients) 52 China, 1 USA Case-control/cohort, case-series, cross-sectional The methodological quality of included rcts was evaluated according to Cochrane Collaboration Risk of Bias Tool. The methodological quality included observational studies was assessed according to the Newcastle-Ottawa Scale. All 53 studies were rated as relatively good quality, range 5-8. AMSTAR2: Moderate quality	COVID-19	Myocardial injury	Incidence (95% CI) Myocardial injury N=53 studies (7,679 patients) 0.21 (0.17-0.25) I^2=97% Myocardial injury in non-survivors N=8 studies (380 patients) 0.66 (0.54-0.78) I^2=86% RR (95% CI) Myocardial injury in severe vs non-severe COVID cases N=29 studies (4,233 patients) 5.74 (3.74-8.79) I^2=87%
Gulsen, Yigitbas[69] December 2019 to April 15, 2020 N=16 studies (11,322 patients) in quantitative analyses 14 China, 1 USA, 1 CDC report (unknown) Case-control/cohort, cross-sectional Newcastle-Ottawa scale, range 5-8 (out of 9) AMSTAR2: Moderate quality	Smoking	Prevalence of smokers stratified for severity (Studies classified COVID-19 cases broadly as follows: (i) mild to moderate: mild, non-severe, common type, did not require ICU care, and COVID-19 survivors and (ii) severe: severe, critical, required ICU care, and non-survivors.)	OR (95% CI) History of smoking Severe vs non-severe COVID N=16 studies (10,797 patients) 2.17 (1.37-3.46) I^2=71% Severe COVID Current smoker vs non-smoker N=10 studies (9,372 patients) 1.51 (1.11-2.05) I^2=49%
Hamam, Goda[81] Search dates NR	COVID-19	Incidence of arrhythmia	Incidence (95% CI) N=9 studies (1,445 patients) 0.20 (0.12-0.28) I^2=95%

N=9 studies (1,445 patients) 8 China, 1 USA Case-control/cohort Newcastle-Ottawa scale, range 7-8 (out of 9) AMSTAR2: Moderate quality			
Hammoud, Bendari[82] December 2019 to August 15, 2020 N=50 studies (430 patients) 16 USA, 10 China, 6 Germany, 5 Italy, 2 Switzerland, 1 Iran, 1 Finland, 1 Austria, 1 Belgium, 1 Japan, 1 Spain, 1 Netherlands, 1 UK, 1 Romania, 1 Austria, 1 Denmark Case-control/cohort, cross-sectional, case report Newcastle-Ottawa Scale (modified) 4 Fair (26-50%) 26 Good (51-75%) 20 Excellent (>76%) AMSTAR2: Critically low quality	COVID-19 mortality	Histopathologies of the heart	In the 23 articles that described cardiac pathology, the most reported pathology was myocardial hypertrophy (87 cases, 51%), followed by myocardial fibrosis (85 cases, 50%), coronary small vessel disease (44 cases, 26%) myocardial cell infiltrate (27 cases, 16%), cardiac amyloidosis (10 cases, 6%), and myocardial necrosis (9 cases, 5%).
Han, Diao[23] Inception to March 7, 2020 N=14 studies (1,800 patients) 14 China Case-control/cohort, case-series Newcastle-Ottawa Scale (0-8 points) and CARE statement (0-8 points), all high quality (≥ 5)	Hypertension CVD Diabetes Cerebrovascular disease Chronic renal disease	Severe COVID (mechanical ventilation, ICU admission or mortality)	OR (95% CI) Hypertension N=6 studies (655 patients) 2.86 (1.83-4.47) I^2=1% CVD N=5 studies (539 patients) 3.53 (1.89-6.58) I^2=0% Diabetes mellitus N=6 studies (655 patients) 3.10 (0.79-12.07) I^2=78% Cerebrovascular disease N=2 studies (254 patients)

AMSTAR2: Critically low quality			2.53 (0.87-7.41) I^2=0% Chronic renal disease N=5 studies (505 patients) 2.29 (0.84-6.25) I^2=0%
Hessami, Shamshirian[51] Inception to May 27, 2020 N=56 studies (29,056 patients) Primary study origin NR Case-control/cohort, case series Newcastle-Ottawa Scale, all low risk of bias for selection and outcome AMSTAR2: Low quality	Acute cardiac injury Heart failure Arrhythmia Hypertension CVD CHD	Mortality	OR (95% CI) Acute cardiac injury N=12 studies 13.29 (7.35-24.0) I^2=74% Heart failure N=8 studies 6.72 (3.34-13.52) I^2=87% Arrhythmia N=3 studies 2.75 (1.43-5.25) I^2=0% Hypertension N=31 studies 2.60 (2.11-3.19) I^2=74% CVD N=14 studies 2.61 (1.89-3.62) I^2=56% CHD N=16 studies 3.78 (2.42-5.90) I^2=76% Prevalence of acute cardiac injury in ICU N=8 studies 0.33 (0.24-0.43) I^2=51%
Hu, Sun[52] Inception to March 10, 2020 N=21 studies (47,344 patients) 20 China, 1 Singapore Case-control/cohort Newcastle-Ottawa Scale, range 5-8 (out of 9) AMSTAR2: Moderate quality	COVID-19	Acute cardiac injury Severe COVID	Incidence (95% CI) Acute cardiac injury N=4 studies 0.06 (0.01-0.11) I^2=72%
Islam, Barek[4]	Comorbidity Hypertension	Mortality	OR (95% CI)

January 1, 2020, to May 17, 2020 N=85 studies (67,299 patients) 69 China, 8 USA, 6 Italy, 1 South Korea, 1 Iran Case-control/cohort Newcastle-Ottawa scale, range 5-8 (out of 9) 83 High quality (6-8), 2 Moderate (5) AMSTAR2: Moderate quality	CVD Diabetes mellitus Cerebrovascular disease Renal disease Liver disease		Any comorbidity N=6 studies (927 patients) 3.46 (2.56-4.67) I^2=0% Hypertension N=19 studies (47,797 patients) 3.16 (2.51-3.97) I^2=44% CVD N=20 studies (47,685 patients) 4.67 (3.22-6.77) I^2=54% Diabetes mellitus N=21 studies (47,864 patients) 2.45 (1.82-3.30) I^2=49% Cerebrovascular disease N=13 studies (2,183 patients) 5.84 (3.63-9.39) I^2=8% Renal disease N=9 studies (1,977 patients) 5.62 (3.34-9.46) I^2=0% Liver disease N=8 studies (1,350 patients) 2.81 (1.31-6.01) I^2=0%
Izcovich, Ragusa[53] Inception to April 28, 2020 N=207 studies (75,607 patients) China, USA, Canada, Spain, France, Turkey, Korea, Japan, Italy, Germany, India and Singapore Primary study design NR Quality in Prognosis Studies tool (QUIPS) Risk of bias was high across most identified studies. Only 7 were low risk of bias. The remaining presented important limitations in at least one domain or item. AMSTAR2: Low quality	Smoking Any chronic condition or comorbidity Cerebrovascular disease Chronic kidney disease (Renal disease) CVD (CHD or Heart failure) Cardiac arrhythmia Arterial hypertension Diabetes mellitus Obesity Dyslipidaemia	Mortality Severe COVID-19* *based on primary study definitions	OR (95% CI) Current smoker Mortality: N=16 studies (12,025 patients) 1.57 (1.19-2.07) Severe COVID-19: N=45 studies (9,147 patients) 1.65 (1.25-2.17) Comorbidity Mortality: N=16 studies (4,406 patients) 3.3 (2.18 to 5) Severe COVID-19: N=40 studies (6,640 patients) 3.16 (2.71-3.68) Cerebrovascular disease Mortality: N=26 studies (15,294 patients) 2.85 (2.02 to 4.01) Severe COVID-19: N=42 studies (11,050 patients) 2.67 (1.84-3.87)

			Renal disease Mortality: N=28 studies (23,448 patients) 2.27 (1.69 to 3.05) Severe COVID-19: N=42 studies (12,056 patients) 2.21 (1.51-3.24) CVD (CHD or Heart failure) Mortality: N=51 studies (37,156 patients) 2.12 (1.77 to 2.56) Severe COVID-19: N=73 studies (16,679 patients) 3.34 (2.71-4.1) Cardiac arrhythmia Mortality: N=6 studies (37,156 patients) 2.13 (1.72 to 2.65) Severe COVID-19: N=4 studies (747 patients) 16.51 (6.69-40.77) Arterial hypertension Mortality: N=52 studies (31,341 patients) 2.02 (1.71 to 2.38) Severe COVID-19: N=94 studies (20,817 patients) 2.5 (2.21- 2.92) Diabetes mellitus Mortality: N=52 studies (31,341 patients) 1.84 (1.61 to 2.1) Severe COVID-19: N=97 studies (21,381 patients) 2.51 (2.2-2.87) Obesity Mortality: N=3 studies (8,922 patients) 1.41 (1.15-1.74) Severe COVID-19: N=8 studies (1,140 patients) 3.74 (2.37-5.89) Dyslipidaemia Mortality: N=4 studies (11,273 patients) 1.26 (1.06-1·5) Severe COVID-19: N=4 studies (559 patients)

			0.63 (0.22-1.83)
Jain, Yuan[18] January 1, 2019, to March 5, 2020 N=7 studies (1,813 patients) 7 China Case-control/cohort STROBE Checklist: 1 Study <55% criteria met 4 studies 55-65% criteria met 2 studies >65% criteria met AMSTAR2: Low quality	CVD Hypertension Diabetes mellitus	Severe COVID ICU admission	OR (95% CI) CVD Severe COVID-19: N=3 studies (53 patients) 2.70 (1.52–4.80) ICU: N=3 studies (75 patients) 4.44 (2.64–7.47) Hypertension Severe COVID-19: N=3 studies (212 patients) 1.97 (1.40–2.77) ICU: N=3 studies (214 patients) 3.65 (2.22–5.99) Diabetes mellitus Severe COVID-19: N=3 studies (105 patients) 3.12 (1.00–9.75) ICU: N=3 studies (103 patients) 2.72 (0.70–10.6)
Khan, Khan[42] December 1, 2019 to April 31, 2020 N=41 studies (27,670 patients) 29 China, 4 Italy, 3 USA, 1 Australia, 1 Mexico, 1 Iran, 1 UK, 1 Korea Case-control/cohort Newcastle-Ottawa Scale, range 5-8 AMSTAR2: Low quality	CVD Cerebrovascular disease Renal disease Liver diseases Hypertension Heart failure Arrhythmia	Mortality	OR (95% CI) Cerebrovascular disease N=15 studies 4.12 (3.04-5.58) I^2=26% Renal disease N=21 studies 3.02 (2.60-3.51) I^2=56% Liver diseases N=13 studies 2.35 (1.50-3.69) I^2=0% CVD N=32 studies 3.42 (2.86-4.09) I^2=84% Hypertension 3.36 (2.64-4.28) Heart failure 4.72 (3.19-6.97) Arrhythmia 3.89 (2.51-6.02)
Kumar, Arora, Clinical Features[55]	Comorbidity Diabetes mellitus	Severe clinical course (Patients in the	OR (95% CI)

January 1, 2020 and March 17, 2020 N=58 studies; 21 in meta-analyses (6,892 patients; 3,496 in meta-analyses) 53 China, 1 Hong Kong, 1 Singapore, 1 South Korea, 1 Australia, 1 Europe Case-control/cohort NIH tool, range 6-9 (50 good quality, 8 f fair quality, 0 poor quality). AMSTAR2: Critically low quality	Hypertension CVD	primary studies with severe COVID-19, ICU, and/or mortality are labelled severe clinical course)	Comorbidity N=12 studies 3.16 (2.32-4.29) I^2=29% Diabetes mellitus N=14 studies 3.11 (1.99-4.88) I^2=48% Hypertension N=13 studies 2.30 (1.84-2.89) I^2= 3% CVD N=13 studies 3.88 (2.30-6.54) I^2=26%
Kumar, Arora, Diabetes[54] January 01, 2020 to April 22, 2020 N=33 studies (16,003 patients) 30 China, 2 USA, 1 France Case-control/cohort NIH tool, range 7-9 (out of 12); 32 good quality, 1 study fair quality. AMSTAR2: Low quality	Diabetes mellitus	Severe clinical course* Severe COVID as labelled in primary studies Mortality *Patients in the primary studies with severe COVID-19, ICU, and/or mortality are labelled severe clinical course.	OR (95% CI) Diabetes mellitus and severe clinical course N=33 studies 2.49 (1.98-3.14) I^2=63% Diabetes mellitus and severe COVID N=24 studies 2.75 (2.09-3.62) I^2=63% Diabetes mellitus and mortality N=9 studies 1.90 (1.98-3.14) I^2=32%
Li, Guan[19] January 01, 2020 to April 14, 2020 N=10 studies (3,118 patients) 10 China Case-control/cohort, case-series Newcastle-Ottawa scale, range 6-8 AMSTAR2: Low quality	CVD Acute cardiac injury	In-hospital mortality	OR (95% CI) CVD N=8 studies 4.85 (3.06-7.70) I^2=29% Acute cardiac injury N=8 studies 21.15 (10.19-43.94) I^2=71%
Li, He[20] January 01, 2020 to April 14, 2020	Smoking Acute cardiac injury	Severe COVID (ICU vs No ICU)	OR (95% CI) Smoking history Fixed effect N=5 studies

N=12 studies (2,445 patients) 12 China Case-control/cohort Newcastle-Ottawa scale, range 6-8 AMSTAR2: Low quality			1.70 (1.20-2.41) I^2=43% Random effect N=5 studies 1.62 (0.79-3.36) I^2=43% Acute cardiac injury Fixed effect N=3 studies 3.38 (1.50-7.60) I^2=78% Random effect N=3 studies 4.35 (0.47-40.00) I^2=78%
Li, Huang[12] January 01, 2020 to April 6, 2020 N=212 studies (281,461 patients) 180 China, 8 USA, 6 South Korea, 3 Singapore, 3 Italy, 3 Taiwan, 2 UK, 2 Hong Kong, 1 Canada, 1 Japan, 1 Vietnam, 2 multi-country Case-control/cohort, case-series Newcastle-Ottawa Scale, range 4-9 (average 7) AMSTAR2: Low quality	Diabetes mellitus Smoking Cerebrovascular disease CVD Hypertension Cardiac failure	Severe COVID* Mortality *Severe COVID-19 disease definition based on the WHO Interim Guidance Report or IDSA/ATS criteria for severe pneumonia	Meta-regression coefficient (95% CI) Diabetes mellitus and severe COVID 23.4 (14.99-31.7) P<0.0001 Smoking severe COVID -1.4 (9.7-6.9) P=0.7 Cerebrovascular disease severe COVID 19.6 (2.6-36.6) P=0.02 CVD and severe COVID 2.0 (3.4-7.4) P=0.5 Hypertension and severe COVID 5.1 (1.1-9.1) P=0.01 Cardiac failure and severe COVID -37.2 (-81.2-6.7) P=0.1 Diabetes mellitus and mortality 8.2 (2.4-13.99) P=0.006 Smoking and mortality -10.3 (29.7-9.2) P=0.3 Cerebrovascular disease and mortality 0.8 (6.0-7.7) P=0.8 Chronic heart disease and mortality 3.7 (0.96-8.4) P=0.1 Hypertension and mortality 6.99 (3.3-10.7) P=0.0002 Cardiac failure and mortality 6.2 (2.3-10.1) P=0.002

Liu, Chen[21] April 5, 2020 N=24 studies (10,948 patients) 20 China, 2 USA, 1 Italy, 1 France Primary study design NR Newcastle-Ottawa Scale, range 6-8 AMSTAR2: Low quality	Diabetes mellitus Hypertension CVD/CAD	Severe COVID* ICU admittance Mortality *as defined in primary studies	OR (95% CI) Comorbidity and Severe COVID 3.50 (1.78-6.90) I^2=61% Comorbidity and ICU 3.36 (1.67-6.76) I^2=36% Comorbidity and mortality 2.09 (0.26 to 16.67) Diabetes mellitus and severe COVID N=10 studies 2.61 (1.93-3.52) I^2=27% Hypertension and severe COVID N=9 studies 2.84 (2.22-3.63) I^2=37% CVD and severe COVID N=8 studies 4.18 (2.87-6.09) I^2=32%
Liu, Zhang[70] Inception to April 13, 2020 N=36 studies (6,395 patients) 36 China Case-control/cohort, case series Newcastle-Ottawa scale, range 4-6 (31 studies =5, 4 studies=6, 1 study=4) AMSTAR2: Critically low quality	Renal disease	Severe COVID	OR (95% CI) Renal disease 3.28 (2.00-5.37) I^2=0% N=13 studies (3,325 patients)
Lu, Zhong[56] April 11, 2020 N=10 studies (11,818 patients) 7 China, 1 Italy, 1 Korea, 1 USA Case-control/cohort, case-series Newcastle-Ottawa Scale, range 5-9	Comorbidity Hypertension Diabetes mellitus	Mortality	OR (95% CI) Comorbidity N=7 studies (2,517 patients) 3.50 (2.35-5.20) I^2=45% Hypertension N=6 studies (3,342 patients) 3.25 (2.15-4.91) I^2=69% Diabetes mellitus N=5 studies (2,307 patients) 2.63 (1.45-4.76) I^2=64%

AMSTAR2: Moderate quality			
Luo, Fu[1] December 2019 to July 2020 N=124 studies 86 China, 10 USA, 7 Italy, 5 Korea, 2 Spain, 2 Switzerland, 2 Iran, 1 UK, 1 France, 1 Bolivia, 1 Egypt, 1 Greece, 1 Israel, 1 Netherlands, 1 Asia, EU, and USA, 1 Poland, 1 Japan Primary study design NR Newcastle-Ottawa scale, range 5-8 (out of 9) AMSTAR2: Moderate quality	Hypertension Diabetes mellitus CVD Renal disease Acute cardiac injury	Severe COVID* Mortality *as defined in primary studies	OR (95% CI) Hypertension Severe COVID: N=55 studies 2.56 (2.12-3.11) I^2=83% Mortality: N=58 studies 2.50 (2.02-3.11) I^2=93% Diabetes mellitus Severe COVID: N=58 studies 2.54 (1.89-3.41) I^2=89% Mortality: N=63 studies 2.50 (2.02-3.11) I^2=93% CVD Severe COVID: N=29 studies 3.86 (2.70-5.52) I^2=63% Mortality: N=30 studies 2.65 (1.86-3.78) I^2=86% Renal disease Severe COVID: N=28 studies 2.20 (1.26-3.85) I^2=77% Mortality: N=35 studies 3.07 (2.43-3.88) I^2=73% Acute cardiac injury Severe COVID: N=11 studies 6.57 (3.70-11.65) I^2=75% Mortality: N=14 studies 16.97 (7.87-36.57) I^2=89%
Ma, Gu[13] Inception to February 25, 2020 N=30 studies (53,000 patients) 27 China, 1 USA, 1 Australia, 1 South Korea Case-control/cohort Agency for Healthcare Research and Quality, range 5-10 AMSTAR2: Low quality	Hypertension Diabetes mellitus CVD Cerebrovascular disease Renal disease	Severe COVID Mortality	OR (95% CI) Hypertension Severe COVID: N=10 studies (2,511 patients) 2.06 (1.61-2.62) I^2=36% Mortality: 4.48 (3.69-5.45) Diabetes mellitus Severe COVID: N=10 studies (2,511 patients) 2.49 (1.82-3.40) I^2=44% Mortality: 4.43 (3.49-5.62) CVD Mortality: 6.75 (5.40-8.43)

			Cerebrovascular disease Severe COVID: N=5 studies (2,197 patients) 3.22 (1.49-6.97) I^2=0% Mortality: 5.34 (2.34-12.16) Renal disease Severe COVID: N=4 studies (1,620 patients) 6.02 (2.19-16.51) I^2=0% Mortality: 9.02 (3.81-21.36)
Mantovani, Byrne[64] January 1, 2020 to May 15, 2020 N=83 studies (78,874 patients) 62 Asia, 21 Europe, Australia, USA Case-control/cohort Newcastle-Ottawa scale, range 5-6 AMSTAR2: Moderate quality	Diabetes mellitus	Severe COVID* In-hospital mortality *as defined in primary studies	OR (95% CI) Diabetes mellitus and severe COVID N=22 studies 2.10 (1.71-2.57) I^2=42% Diabetes mellitus and mortality N=15 studies 2.68 (2.09-3.44) I^2=47%
Mao, Lin[57] October 1, 2019 to July 26, 2020 N=17 studies (1,310 patients) 13 China, 1 England, 1 France, 1 South Korea, 1 Turkey Case-control/cohort Newcastle-Ottawa Study for cohort studies (12 moderate quality and 4 high quality) and AHRQ for cross-sectional studies (1 moderate quality) AMSTAR2: Critically low quality	Amongst patients with COVID-19 and diabetes mellitus: Hypertension CVD Cerebrovascular disease For all patients: Diabetes mellitus	Mortality Severe COVID Cardiac injury	OR (95% CI) Patients with COVID-19 and diabetes mellitus: Hypertension and mortality N=3 studies (288 patients) 0.60 (0.12-3.11) I^2=47% CVD and mortality N=3 studies (288 patients) 0.44 (0.17-1.19) I^2=52% Cerebrovascular disease and mortality N=2 studies (201 patients) 0.32 (0.10-1.02) I^2=0% All patients: Diabetes mellitus and mortality N=14 studies (3,699 patients) 2.52 (1.77-3.58) I^2=58%

			Diabetes mellitus and severe COVID N=9 studies (2,366 patients) 2.66 (2.12-3.32) I^2=33% Diabetes mellitus and cardiac injury N=7 studies (2,154 patients) 2.13 (1.66-2.73) I^2=47%
Matsushita, Ding[59] December 1, 2019 to April 3, 2020 N=25 studies (76,638 patients) 21 China, 3 USA, 1 Italy Case-control/cohort, cross-sectional Newcastle-Ottawa Scale, range 5-9 AMSTAR2: Moderate quality	Smoking Hypertension Diabetes mellitus CVD	Severe COVID (all-cause mortality, ICU admission, ARDS, or the need for mechanical ventilation)	OR (95% CI) Current vs. never smoking N=3 studies 1.82 (0.83-3.96) I^2=58% Former vs. never smoking N=3 studies 2.95 (1.15-7.53) I^2=65% Hypertension N=8 studies 3.08 (2.33-4.07) I^2=41% Diabetes mellitus N=9 studies 3.55 (2.56-4.93) I^2=61% CVD N=10 studies 5.05 (4.36-5.85) I^2=0%
Momtazmanesh, Shobeiri[60] Inception to April 21, 2020 N=54 studies Primary data origin NR Case-control/cohort, case-series, case-reports Newcastle-Ottawa scale, range 5-8 AMSTAR2: Moderate quality	Diabetes mellitus Hypertension CVD Acute cardiac injury	Prevalence of new-onset CV conditions - Acute cardiac injury - Arrhythmia - Heart failure Mortality	Prevalence % (95% CI) Acute cardiac injury N=16 studies (2,647 patients) 25.3 (19.5-31.1) I^2=93% Arrhythmia N=4 studies (444 patients) 26.1 (5.9-46.1) I^2=97% Heart failure N=2 studies (367 patients) 23.7 (19.3-28.0) I^2=0% OR (95% CI) Acute cardiac injury and mortality N=7 studies (1,046 patients) 19.64 (10.28-37.53) I^2=64% CVD and mortality N=6 studies (550 patients) 7.87 (2.117-28.57) I^2=54%

			Hypertension and mortality N=8 studies (1,033 patients) 2.49 (2.02-3.07) I^2=25% Diabetes mellitus and mortality N=6 studies (682 patients) 1.66 (1.20-2.29) I^2=0%
Moula, Micali[61] December 1, 2019 to May 18, 2020 N=26 studies (8,497 patients) 20 China, 2 Italy, 2 Korea, 1 Iran, 1 USA Case-control/cohort, case-series ROBINS-I tool, overall bias ratings were: 10 Critical, 6 Serious, 11 Moderate (one paper split into two cohorts = '27 studies') AMSTAR2: Low quality	CVD and CAD Hypertension Cerebrovascular disease Diabetes mellitus	Mortality	RR (95% CI) CVD/CAD N=26 studies 1.96 (1.51-2.54) Hypertension N=24 studies 1.73 (1.37-2.19) Cerebrovascular disease N=15 studies 1.76 (1.25-2.50) Diabetes mellitus N=26 studies 1.59 (1.25-2.02)
Nannoni, de Groot[14] December 1, 2019 to September 14, 2020 N=145 studies (108,571 patients) 12 North America, 6 EU, 6 Asia Case-control/cohort, case-series, case-reports Newcastle-Ottawa Scale, 14 High quality, 19 Moderate quality. AMSTAR2: Critically low quality	Severe COVID-19 Hypertension Diabetes mellitus CAD	Acute cerebrovascular disease	Proportion % (95% CI) Acute cerebrovascular disease N=24 studies (108,571 patients) 1.4 (1.0–1.9) I^2=95% OR (95% CI) Hypertension and acute cerebrovascular disease N=4 studies (11,683 patients) 7.35 (1.94-27.87) I^2=76% Diabetes mellitus and acute cerebrovascular disease N=4 studies (11,683 patients) 5.56 (3.34-9.24) I^2=22% CAD and acute cerebrovascular disease N=2 studies (2,181 patients) 3.12 (1.61-6.02) I^2=0% Severe COVID and acute cerebrovascular disease N=3 (2,389)

			5.10 (2.72-9.54) I^2=0%
Nasiri, Haddadi[78] January 1, 2019 to May 29, 2020 N=34 studies (5,057 patients) 32 China, 1 Germany, 1 Norway Case-control/cohort, case-series, case-reports, cross-sectional Joanna Briggs Institute (JBI) checklist, all classified as low risk of bias. AMSTAR2: Moderate quality	COVID-19	Acute cardiac injury	Pooled frequency (95%CI) Acute cardiac injury N=243 patients 12.4 (6.2-23.2) I^2=65%
Noor, Islam[3] January 1, 2020 to August 11, 2020 N=58 studies (122,191 patients) 26 China, 8 USA, 7 Italy, 4 Spain, 2 South Korea, 2 Mexico, 1 Bangladesh, 1 Brazil, 1 UK, 1 Greece, 1 Iran, 1 Kuwait, 1 Switzerland, 1 Turkey, 1 EU Case-control/cohort Newcastle-Ottawa scale, range 6-9 AMSTAR2: Moderate quality	Obesity Smoking Hypertension Diabetes mellitus CVD Cerebrovascular disease CHD Renal disease Liver disease	Mortality	RR (95% CI) Obesity N=7 studies (13,477 patients) 2.18 (1.10–4.34) I^2=99% Smoking N=10 studies (13,598 patients) 1.81 (0.99–3.33) I^2=99% Hypertension N=38 studies (37,785 patients) 2.08 (1.79–2.43) I^2=98% Diabetes mellitus N=35 studies (35,411 patients) 1.87 (1.23–2.84) I^2=100% CVD N=16 studies (8,925 patients) 2.51 (1.20–5.26) I^2=100% Cerebrovascular disease N=11 studies (6,069 patients) 2.75 (1.54–4.89) I^2=99% CHD N=11 studies (10,851 patients) 3.63 (1.52–8.65) I^2=100% Renal disease N=16 studies (24,450 patients)

			2.11 (1.72–2.58) I^2=97% Liver disease N=8 studies (7,090 patients) 2.02 (1.16–3.50) I^2=95%
Palaiodimos, Chamorro-Pareja[65] May 10, 2020 N=14 studies (18,506 patients) 5 Asia, 5 USA, 4 EU Case-control/cohort Quality in Prognosis Studies (QUIPS) tool, all low risk of bias AMSTAR2: Moderate quality	Diabetes mellitus	Mortality	OR (95% CI) Diabetes mellitus N=14 studies (18,506 patients) 1.65 (1.35-1.96) I^2=77%
Parohan, Yaghoubi[62] Inception to May 1, 2020 N=14 studies (29,909 patients) 12 China, 1 Italy, 1 Iran Case-control/cohort Newcastle-Ottawa scale, range 5-8 AMSTAR2: Critically low quality	Hypertension CVD Diabetes mellitus	Mortality	OR (95% CI) Hypertension N=8 studies 2.70 (1.40-5.24) I^2=93% CVD N=9 studies 3.72 (1.77-7.83) I^2=89% Diabetes mellitus N=7 studies 2.41 (1.05-5.51) I^2=94%
Parveen, Sehar[22] Inception to March 31, 2020 N=7 studies (2,018 patients) 7 China Case-control/cohort, case-series NIH Quality Assessment tool, 4 Good, 3 Fair AMSTAR2: Critically low quality	Diabetes mellitus Hypertension	Prevalence in of diabetes mellitus/hypertension	OR (95% CI) Diabetes mellitus in non-survivors vs. survivors N=2 studies 0.56 (0.35-0.90) I^2=0% Diabetes mellitus in ICU vs non-ICU N=2 studies 0.78 (0.06-9.34) I^2=76% Hypertension in non-survivors vs survivors N=2 studies 0.50 (0.34-0.73) I^2=0%

			Hypertension in ICU vs non-ICU N=2 studies 0.42 (0.22-0.81) I^2=0%
Patanavanich, Glantz[71] January 1, 2020 to May 25, 2020 N=47 studies (31,871 patients) 33 China, 8 USA, 3 Italy, 1 UK, 1 South Korea, 1 International Case-control/cohort, case-series Modified ACROBAT-NRSI tool, range 0-1.6 AMSTAR2: Moderate quality	Smoking	Severe COVID* Mortality *Respiratory distress with respiratory rate ≥30/min, or oxygen saturation ≤93% at rest, or oxygenation index ≤300 mmhg.	OR (95% CI) Smoking and severe COVID N=47 studies 1.56 (1.32-1.83) I^2=45% Smoking and mortality N=8 studies 1.19 (1.05-1.34) I^2=0%
Patel, Malik, Shah[72] December 1, 2019 to April 30, 2020 N=11 studies (4,987 patients) Primary study origin NR Case-control/cohort Newcastle-Ottawa Scale, range 4-6 Cochrane's Collaboration Tool (3 high risk of bias, 8 moderate risk of bias) AMSTAR2: Critically low quality	Cerebrovascular disease	ICU admission Mechanical ventilation Mortality Composite outcome	OR (95% CI) ICU admission unadjusted N=7 studies (3,901 patients) 1.54 (1.25-1.62) I^2=95% ICU admission age-adjusted N=7 studies (3,901 patients) 1.82 (1.25-2.69) I^2=94% Mechanical ventilation unadjusted N=8 studies (2,196 patients) 1.32 (1.13-1.55) I^2=91% Mechanical ventilation age-adjusted N=8 studies (2,196 patients) 1.33 (1.09-1.63) I^2=93% Mortality unadjusted N=8 studies (4,240 patients) 1.45 (1.22-1.72) I^2=96% Mortality age-adjusted N=8 studies (4,240 patients) 1.42 (1.14-1.77) I^2=96% Composite outcome 2.67 (1.75-4.06) I^2=12%
Patel, Malik, Usman[39]	Smoking Diabetes mellitus Hypertension	Mortality Mechanical ventilation	OR (95% CI) Smoking

December 1, 2019 to May 31, 2020 N=29 studies (12,258 patients) 19 China, 5 USA, 2 Singapore, 1 Australia, 1 Europe, 1 South Korea Case-control/cohort Newcastle-Ottawa Scale, 12 high risk of bias, 17 moderate risk of bias AMSTAR2: Critically low quality	Cerebrovascular disease Chronic liver disease CVD Cardiac complications		Mechanical ventilation 0.9 (0.88-0.97) I^2=94% Mortality 0.95 (0.93-0.98) I^2=81% Diabetes mellitus Mechanical ventilation 1.02 (0.94-1.11) I^2=96% Mortality 1.02 (0.93-1.12) I^2=96% Hypertension Mechanical ventilation 1 (0.94-1.11) I^2=96% Mortality 1.01 (0.93-1.09) I^2=96% Cerebrovascular disease Mechanical ventilation 1.42 (1.14-1.77) I^2=96% Mortality 1.34 (1.09-1.63) I^2=93% Chronic liver disease Mechanical ventilation 1.08 (1.01-1.17) I^2=96% Mortality 1.08 (1.03-1.17) I^2=94% CVD Mechanical ventilation 0.99 (0.88-1.12) I^2=96% Mortality 1.32 (1.1-1.58) I^2=90% Cardiac complications Mechanical ventilation 1.01 (0.92-1.11) I^2=95% Mortality 0.98 (0.9-1.06) I^2=95%
Porto, Iamonti[24] Inception to April 2020 N=5 studies (1,453 patients) 5 China Primary study design NR Jedad scale, only studies scoring $\geq$2 points were	Diabetes mellitus	Mortality	OR (95% CI) Diabetes mellitus 8.9 (4.5-17.4)

included and considered high quality AMSTAR2: Critically low quality			
Reddy, Charles[6] December 1, 2019 to June 2, 2020 N=47 studies (32,849 patients) 32 China, 10 USA, 2 International, 1 UK, 2 Italy Case-control/cohort Newcastle-Ottawa scale, 22 Good quality, 6 Fair quality, 19 Poor quality AMSTAR2: High quality	Current smoking vs. Former/never Smoking history vs. Never	Severe or critical COVID Mortality Disease progression ICU admission Mechanical ventilation	RR (95% CI) Current smoking Severe/critical COVID: N=8 studies (2,100 patients) 1.98 (1.16-3.38) I^2=87% Mortality: N=7 studies (14,741) 1.46 (0.83-2.60) I^2=81% N=7 (14,741 patients) Disease progression: N=3 studies (458 patients) 1.54 (0.52-4.58) I^2=81% ICU admission: N=6 studies (2,368 patients) 0.72 (0.42-1.24) I^2=40% Mechanical ventilation: N=5 studies (1,585 patients) 1.13 (0.75-1.72) I^2=32% Smoking history Severe/critical COVID: N=15 studies (4,007 patients) 1.35 (1.19-1.53) I^2=19% Mortality: N=9 studies (14,105 patients) 1.26 (1.20-1.32) I^2=0% Disease progression: N=5 studies (468 patients) 2.18 (1.06-4.49) I^2=69% ICU admission: N=4 studies (1,802 patients) 1.12 (0.96-1.31) I^2=0% Mechanical ventilation: N=4 studies (917 patients) 1.20 (1.01-1.42) I^2=0%
Rhim, Park[43] Inception to May 1, 2020 N=23 studies (227,856 patients) 19 China, 1 Italy, 1 Spain, 1 USA, 1 Korea Case-control/cohort, cross-sectional, case series	Diabetes mellitus Hypertension CVD Cerebrovascular disease Chronic liver disease Renal disease Acute cardiac injury	Mortality	OR (95% CI) Diabetes mellitus 2.53 (1.77-3.61) I^2=66% N=15 studies (206,488 patients) Hypertension 2.88 (2.22-3.73) I^2=7% N=11 studies (1,246 patients) CVD 5.06 (3.54-7.24) I^2=46%

Newcastle-Ottawa Scale, range 7-9 AMSTAR2: Low quality			N=14 studies (206,287 patients) Cerebrovascular disease 4.83 (2.61-8.93) I^2=34% N=9 studies (1,306 patients) Chronic liver disease 1.36 (0.68-2.74) I^2=1% N=6 studies (812 patients) Renal disease 6.32 (3.62-11.03) I^2=0% N=8 studies (1,500 patients) Acute cardiac injury Cases: 43% 22.7 (4.81-107.2) I^2=81% N=4 studies (582 patients)
Roncon, Zuin[66] Inception to March 25, 2020 N=8 studies (1,382 patients) Primary study origin NR Primary study design NR Newcastle-Ottawa Scale, 7 high quality (>7 stars), 1 moderate quality (5-7 stars) AMSTAR2: Critically low quality	Diabetes mellitus	ICU admission Mortality	OR (95% CI) Diabetes mellitus and ICU admission N=4 studies (114 patients) 2.79 (1.85-4.22), I^2=46% Diabetes mellitus and mortality N=4 (354 patients) 3.21 (1.82, 5.64) I^2=16%
Sabatino, De Rosa[7] December 1, 2019 to June 11, 2020 N=21 studies (77,317 patients) 11 China, 5 USA, 1 Italy, 1 UK, 1 Singapore, 1 Korea, 1 Iran Primary study design NR Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (QAT-OC/CSS) of	COVID-19 Cardiovascular co-morbidity/risk factor Cardiovascular complications	Angina Arrhythmias Myocardial injury Acute Heart failure Myocardial infarction CV complications Mortality	Prevalence % (95% CI) Angina 10.2 (3.2-20.5) Arrhythmias 18.4 (7.8-32.3) Myocardial injury 10.3 (6.7-14.6) Acute Heart failure 2.0 (0.94-3.35) Myocardial infarction 3.5 (2.1-5.3)

the NIH, overall quality rating was judged as Fair AMSTAR2: Moderate quality			Cardiovascular complications 14.1 (10.3-20.2) Associations with mortality, regression coefficient 95%CI Cardiovascular comorbidity 0.004 (0.003-0.005) p<0.001 Cardiovascular complications 0.001 (0.000-0.003) p=0.038
Sales-Peres, Azevedo-Silva[73] Inception to April 27, 2020 N=9 studies (6,577 patients) 3 USA, 2 China, 2 France, 1 Spain, 1 Italy Case-control/cohort, cross-sectional, case series Newcastle-Ottawa Scale, range 6-8 AMSTAR2: Critically low quality	Obesity	Severe complications	RR (95% CI) Obesity N=3 studies (463 patients) 1.40 (0.91-2.17) I^2=38%
Sepandi, Taghdir[25] January 1, 2020 to March 23, 2020 N=13 studies (12,044 patients) 13 China Case-control/cohort Newcastle-Ottawa Scale, 2 Fair, 11 Good AMSTAR2: Critically low quality	Diabetes mellitus Hypertension Renal disease CVD Smoking	Mortality	OR (95% CI) Diabetes mellitus N=9 studies 2.42 (1.06-5.52) I^2=90% Hypertension N=8 studies 2.54 (1.21-5.32) I^2=91% Renal disease N=7 studies 2.61 (1.22-5.60) I^2=78% CVD N=6 studies 4.37 (1.13-16.9) I^2=88% Smoking N=3 studies 1.70 (0.53-5.35) I^2=43%
Shafi, Shaikh[83] Search dates NR	COVID-19	Cardiovascular and cardiac manifestations	Patients with hypertension or any other cardiovascular comorbidity were more likely to develop a

N=61 studies 33 China, 10 USA, 5 Italy, 3 Spain, 2 Germany, 1 International, 1 France and Switzerland, 1 South Korea, 1 France, 1 Belgium, 1 Iran, 1 Trinidad, 1 Brazil Case-control/cohort, case series, case report, RCT Newcastle-Ottawa Scale, range 5-9 AMSTAR2: Low quality			cardiovascular complication due to SARS-CoV-2 infection, with a higher proportion of hypertensive patients developing acute heart injury and heart failure. Patients affected with COVID-19 are at an increased risk of arrhythmias due to underlying comorbidities, polypharmacy, and disease progression. Myocardial injury in COVID-19 is a recognized phenomenon. Case series include reports of myocarditis, ACS, and spontaneous coronary artery dissection. Cardiac biomarkers are important in recognizing patients that might be presenting with early signs of myocardial injury secondary to COVID-19.
Shao, Shang[26] Inception to March 31, 2020 N=9 studies (1,470 patients) 9 China Primary study design NR Newcastle-Ottawa Scale, range 7-8 (7 studies scored 8 and 2 studies scored 7) AMSTAR2: Low quality	Myocardial injury	Mortality	OR (95% CI) Myocardial injury 13.7 (9.8-19.1) I^2=52%
Shi, Wang[44] December 1, 2019 to April 29, 2020 N=27 studies 24 China, 2 USA, 1 Italy Case-control/cohort Quality in Prognostic Factor Studies (QUIPS) tool, range low risk in all categories-high risk in 3 categories	Current smoking Renal disease Cerebrovascular disease CVD Diabetes mellitus Hypertension Chronic liver disease Acute cardiac injury	Mortality	RR (95% CI) Current smoking N=5 studies (2,761 patients) 2.95 (1.32-6.58) I^2=30% Renal disease N=4 studies (2,111 patients) 8.37 (3.94-17.77) I^2=0% Cerebrovascular disease N=4 studies (2,071 patients) 7.66 (3.87-15.2) I^2=0%

AMSTAR2: Low quality			CVD N=5 studies (2,258 patients) 3.16 (2.19-4.56) I^2=17% Diabetes mellitus N=5 studies (2,689 patients) 2.21 (1.37-3.56) I^2=45% Hypertension N=6 studies (2,880 patients) 2.11 (1.49-2.99) I^2=82% Chronic liver disease N=3 studies (2,109 patients) 1.47 (0.63-3.42) I^2=0% Acute cardiac injury N=6 studies (1,207 patients) 8.22 (4.95-13.7) I^2=72%
Sinclair, Zhu[84] December 1, 2019 to May 11, 2020 N=5 studies (1,053 patients) 4 China, 1 USA Primary study design NR Newcastle Ottawa Scale, all 7 (high quality) AMSTAR2: Moderate quality	COVID-19 CVD Hypertension Diabetes mellitus	Cardiac complications	Cardiac complications - prevalence 17% OR (95% CI) – cardiac complications CVD Fixed-effect: 5.12 (3.09-8.48) Random-effect: 3.82 (1.44-10.15) I^2=33% Hypertension Fixed-effect: 4.37 (2.99-6.39) Random-effect: 4.35 (2.96-6.38) I^2=0% Diabetes mellitus Fixed-effects: 2.61 (1.67-4.09) Random-effects: 2.40 (1.51-3.82) I^2=0%
Sreenivasan, Khan[45] November 30, 2019 to March 30, 2019 N=10 studies (1,427 patients) 8 China, 1 Singapore, 1 USA Case-control/cohort Newcastle-Ottawa Scale, range 3-7	COVID-19 Renal disease Chronic liver disease Smoking CVD Cerebrovascular disease	Acute myocardial infarction/injury Arrhythmia Complicated hospital course* *Mortality, ICU admission, acute respiratory distress syndrome, or need	Event rate (95% CI) Acute myocardial infarction/injury 0.079 (0.029-0.197, p<0.001) N=441 patients Arrhythmia 0.167 (0.113-0.238, p<0.001) N=138 patients OR (95% CI) – Complicated hospital course

AMSTAR2: Critically low quality	Diabetes mellitus Hypertension	for invasive mechanical ventilation.	Renal disease N=3 studies 5.12 (1.18-22.19) I^2=0% Chronic liver disease N=2 studies 1.07 (0.30-3.87) Smoking N=2 studies 2.54 (1.00-6.46) CVD N=6 studies 5.82 (2.44-13.85) I^2=28% Cerebrovascular disease N=2 studies 8.30 (1.24-55.4) I^2=0% Diabetes mellitus N=6 studies 2.46 (1.37-4.42) I^2=23% Hypertension N=6 studies 2.09 (1.02-4.27) I^2=74%
Ssentongo, Ssentongo[46] December 1, 2019 to July 9, 2020 N=25 studies (65,484 patients) 19 China, 3 USA, 1 Italy, 1 Africa, 1 International Case-control/cohort, case series Newcastle-Ottawa Scale, range 5-9 (mean 7) AMSTAR2: Moderate quality	CVD Hypertension Cerebral vascular disease Diabetes mellitus Renal disease Chronic liver disease Heart failure	Mortality	RR (95% CI) CVD N=14 studies 2.25 (1.60-3.17) I^2=49% Hypertension N=13 studies 1.82 (1.43-2.32) I^2=70% Cerebral vascular disease N=4 studies 2.16 (0.97-4.80) I^2=64% Diabetes mellitus N=16 studies 1.48 (1.02-2.15) I^2=84% Renal disease N=9 studies 3.25 (1.13-9.28) I^2=99% Chronic liver disease N=3 studies

			1.73 (0.86-3.46) I^2=0% Heart failure N=3 studies 2.03 (1.28-3.21) I^2=0%
Tabrizi, Lankarani[47] Inception to March 12, 2020 N=17 studies (3,189 patients) 16 China, 1 Singapore Case-control/cohort Newcastle Ottawa Scale, range 3-8 AMSTAR2: Critically low quality	Diabetes mellitus Hypertension CVD Renal disease Cerebrovascular accident Liver disease	Severe COVID (as measured by disease severity criteria as severe/critical disease type or admitted to ICU or the use of mechanical ventilation)	OR (95% CI) Diabetes mellitus N=9 studies 3.54 (1.79-7.01) I^2=58% Hypertension N=10 studies 2.35 (1.83-3.02) I^2=0% CVD N=9 studies 2.44 (1.64-3.63) I^2=0% Renal disease N=6 studies 6.38 (3.23-12.59) I^2=0% Cerebrovascular accident N=4 studies 3.94 (0.88-17.59) I_2=53% Liver disease N=6 studies 1.25 (0.35-4.41) I^2=40%
Tamara, Tahapary[11] Inception to April 14, 2020 N=3 studies (806 patients) 1 China, 1 USA, 1 France Case-control/cohort Newcastle Ottawa Scale, range 7-9 AMSTAR2: Moderate quality	Obesity (BMI >25 or 30 kg/m2)	In-hospital critical care	One study demonstrated that COVID-19 patients with obesity grade II had 7.36 (1.63-33.14; p= 0.021) times increased risk of having invasive mechanical ventilation during in-hospital care, compared to non-obese patients with COVID-19. One study stratified patients by age, <60 years and >60 years. Compared to healthy weight and over-weight groups, the rate of hospitalization increased by 2.0 (1.6-2.6; p<0.0001) and 2.2 (1.7-2.9; p< 0.0001) times in the younger patient group with obesity grade I and II, respectively. Another study reported an increased risk of 1.30 (1.09-1.54; p<0.003) times in COVID-19 patients with a

			BMI higher than 25 kg/m^2 to develop severe COVID-19 compared to healthy weight and over-weight patients, however, this was attenuated in multivariate analyses.
Taylor, Hofmeyr[48] January 1, 2020 to April 7, 2020 N=9 studies (1,823 patients) 7 China, 1 USA, 1 Italy Case-control/cohort Newcastle-Ottawa Scale, range 4-6 AMSTAR2: Critically low quality	Hypertension	Mortality in intensive care	OR (95% CI) Hypertension N=3 studies 4.17 (2.90-5.99) I^2=0%
Tian, Jiang[49] January 1, 2020 to April 24, 2020 N=14 studies (4,659 patients) 13 China, 1 USA Primary study design NR Agency for Healthcare Research and Quality (AHRQ) score checklist, 1 low quality, 5 moderate quality, 8 high quality AMSTAR2: Critically low quality	Hypertension CVD Cerebrovascular disease Diabetes mellitus Smoking Renal disease	Mortality	OR (95% CI) Hypertension N=11 studies (4,263 patients) 2.53 (2.07-3.09) I^2=15% CVD N=12 studies (1,842 patients) 3.81 (2.11-6.85) I^2=61% Cerebrovascular disease N=6 studies (948 patients) 4.92 (1.54-15.68) I^2=51% Diabetes mellitus N=12 studies (4,315 patients) 1.97 (1.67-2.31) I^2=0% Smoking N=4 studies (678 patients) 1.77 (0.83-3.81) I^2=8% Renal disease N=6 studies (1,087 patients) 9.41 (3.23-27.40) I^2=0%
Villalobos, Ott[63] Inception to April 29, 2020 N=75 studies 66 China, 5 USA, 2 UK, 1 Iran, 1 France	CVD Cerebrovascular disease Renal disease Diabetes mellitus Liver disease Hypertension	ICU admission Mortality	RR (95% CI) CVD ICU: N=8 studies 2.1 (1.3-3.2) I^2=86% Mortality: N=15 studies 3.3 (2.3-4.5) I^2=86%

Primary study design NR ROBINS-I tool 45 high risk of bias, only few had overall low risk of bias in all categories. AMSTAR2: Moderate quality	Myocardial infarction		Cerebrovascular disease ICU: N=4 studies 1.9 (0.9-4.0) I^2=92% Mortality: N=7 studies 2.6 (1.7-4.1) I^2=61% Renal disease ICU: N=4 studies 2.1 (0.9-4.9) I^2=90% Mortality: N=3 studies 2.5 (1.8-3.4) I^2=0% Diabetes mellitus ICU: N=12 studies 1.9 (1.4-2.6) I^2=90% Mortality: N=18 studies 2.2 (1.7-2.9) I^2=83% Hypertension ICU: N=9 studies 1.4 (1.1-1.7) I^2=53% Mortality: N=17 studies 2.7 (2.1-3.4) I^2=80% Liver disease Mortality: N=3 studies 1.9 (0.6-6.4) I^2=30% Myocardial infarction Mortality: N=5 studies 3.9 (1.5-8.6) I^2=89%
Wang, Deng[27] December, 2019 to March 16, 2020 N=25 studies (4,881 patients) 25 China Case-control/cohort, cross-sectional Newcastle-Ottawa scale, range 3-7 AMSTAR2: Critically low quality	Diabetes mellitus Hypertension CVD Chronic liver disease	Severe COVID	RR (95% CI) Diabetes mellitus N=12 studies (1,740 patients) 1.53 (1.29-1.82) Hypertension N=13 studies (1,781 patients) 1.40 (1.22-1.60) CVD N=12 studies (1,412 patients) 1.79 (1.50-2.13) Chronic liver disease N=8 studies (1,312 patients) 0.93 (0.62-1.42)
Wang, Li[28] Inception to March 1, 2020	Hypertension Diabetes Liver disease	Severe COVID	OR (95% CI)

N=6 studies (1,558 patients) 6 China Case-control/cohort Newcastle-Ottawa Scale, range 6-8 AMSTAR2: Critically low quality	Renal disease CVD Cerebrovascular disease		Hypertension N=6 studies 2.29 (1.69-3.10) I^2=4% Diabetes N=6 studies 2.47 (1.67-3.66) I^2=39% Liver disease N=5 studies 0.67 (0.30-1.49) I^2=0% Renal disease N=4 studies 2.51 (0.93-6.78) I^2=0% CVD N=4 studies 2.93 (1.73-4.96) I^2=0% Cerebrovascular disease N=3 studies 3.89 (1.64-9.22) I^2=45%
Wu, Liu[5] Inception to April 1, 2020 N=41 studies (5,064 patients) 41 China Case-control/cohort Newcastle-Ottawa Scale, range 7-8 (2 studies =7, 39 studies =8) AMSTAR2: Moderate quality	Smoking Alcohol Diabetes mellitus CVD Cerebrovascular disease Hypertension Chronic liver disease BMI	Severe COVID	OR (95% CI) Smoking N=7 studies (1,484 patients) 1.26 (0.69-2.32) Diabetes mellitus N=17 studies (2,476 patients) 2.38 (1.59-3.57) CVD N=13 studies (2,089 patients) 3.16 (2.19-4.56) Cerebrovascular disease N=7 studies (1,213 patients) 3.34 (1.29-8.69) Hypertension N=18 studies (2,510 patients) 2.63 (1.79-3.88) Chronic liver disease N=11 studies (1,982 patients) 0.81 (0.47-1.40) SMD (95% CI) BMI

			N=4 studies (221 patients) 1.27 (-0.88-3.42)
Wu, Tang[29] Inception to April 14, 2020 N=9 studies (926 patients) 9 China Primary study origin NR Newcastle-Ottawa scale, range 7-8 (9 studies=7 and 1 study =8) AMSTAR2: Moderate quality	Diabetes mellitus	Mortality	OR (95% CI) Diabetes mellitus 1.75 (1.31-2.36) I^2=5% Diabetes mellitus (Age ≥70 years) 1.33 (0.78-2.28) I^2=0% Diabetes mellitus (Age <70 years) 2.05 (1.44-2.94) I^2=32%
Wu, Zuo[58] Inception to May 13, 2020 N=73 studies (171,108 patients) 54 China, 4 Italy, 2 USA, 2 UK, 2 France, 2 Spain, 6 'other' Case-control/cohort Agency for Healthcare Research and Quality, 31 high quality, 41 moderate, 1 low AMSTAR2: Critically low quality	Hypertension CVD Arrhythmia Renal disease Smoker Acute cardiac injury	Severe COVID	OR (95% CI) Hypertension N=22 studies 2.40 (2.08-2.78) I^2=39% CVD N=15 studies 3.54 (2.68-4.68) I^2=37% Arrhythmia N=3 studies 14.8 (8.9-24.6) I^2=49% Renal disease N=15 studies 1.84 (1.47-2.30) I^2=26% Smoker N=10 studies 1.61 (1.28-2.02) I^2=0% Acute cardiac injury N=7 studies 11.9 (7.64-18.46) I^2=0% Incidence of acute cardiac injury 6% (3%-9%)
Xu, Mao[30] Inception to March 8, 2020 N=20 studies (4,602 patients) 20 China	BMI Smoker Diabetes mellitus Hypertension CVD	Severe COVID	SMD (95% CI) BMI 3.38 (0.07-6.69) OR (95% CI)

Cross-sectional American Agency for Healthcare Research and Quality, range 3-7 AMSTAR2: Critically low quality			Smoker N=3 studies (412 patients) 1.40 (0.65-3.01) I^2=0% Diabetes mellitus N=10 studies (1,083 patients) 3.04 (2.01-4.60) I^2=20% Hypertension N=10 studies (1,083 patients) 2.31 (1.68-3.18) I^2=47% CVD N=7 studies (906 patients) 2.76 (1.39-5.45) I^2=26%
Youssef, Hussein[31] Inception to April 16, 2020 N=20 studies (3,428 patients) 20 China Case-control/cohort Newcastle-Ottawa scale, 2-8 (1 study =2, 2 studies =3, 6 studies =5, 2 studies =6, 4 studies =7, 5 studies =8) AMSTAR2: Moderate quality	Hypertension Renal disease Diabetes mellitus CVD Chronic liver disease Cerebrovascular disease Myocardial injury	Severe COVID	OR (95% CI) Hypertension 2.36 (1.86-3.01) I^2=14% N=13 studies (2,141 patients) Renal disease 7.28 (3.25-16.16) I^2=0% N=7 studies (1,675 patients) Diabetes mellitus 2.72 (2.05-3.60) I^2=42% N=14 studies (2,193 patients) CVD 5.11 (2.03-12.83) I^2=77% N=12 studies (2,327 patients) Chronic liver disease 1.17 (0.66-2.06) I^2=0% N=9 studies (1,629 patients) Cerebrovascular disease 5.73 (2.52-13.04) I^2=33% N=5 studies (769 patients) Myocardial injury 11.2 (0.44-285.9) I^2=90% N=3 studies (464 patients)
Yu, Wu[74] December 2019 to July 25, 2020 N=31 studies (23,632 patients)	Cardio-cerebrovascular disease	Severe COVID Mortality	OR (95% CI) Cardio-cerebrovascular disease and severe COVID N=20 studies 3.00 (2.10-4.30) I^2=65%

20 China, 4 USA, 2 Brazil, 1 Greece, 1 Iran, 1 Italy, 1 Spain, 1 Oman Case-control/cohort Newcastle-Ottawa scale, range 6-8 (5 studies =6, 19 studies =7, 7 studies =8) AMSTAR2: Moderate quality			Cardio-cerebrovascular disease and mortality N=16 studies 5.59 (2.81-11.11) I^2=94%
Zhang, Shen[8] Inception to May 8, 2020 N=17 studies (1,913 patients) 6 China, 5 France, 3 Italy, 3 Netherlands Case-control/cohort Newcastle-Ottawa scale, range 5-8 (2 studies =5, 1 study =6, 8 studies =7, 6 studies =8) AMSTAR2: Moderate quality	COVID-19 Venous thromboembolism	Incident: - Venous thromboembolism - Pulmonary embolism - Deep vein thrombosis Severe COVID	Incidence (95% CI) Venous thromboembolism 0.25 (0.19-0.31) I^2=96% Pulmonary embolism 0.19 (0.13-0.25) I^2=93% Deep vein thrombosis 0.07 (0.04-0.10) I^2=88% RR (95% CI) Venous thromboembolism and severe COVID 4.76 (2.66-8.50) I^2=47%
Zhang, Wu[32] Inception to March 20, 2020 N=12 studies (2,389 patients) 12 China Case-control/cohort Newcastle-Ottawa scale and STROBE, range 6-8 (6 studies =6, 7 studies =7, 5 studies =8) AMSTAR2: Critically low quality	Hypertension	Severe COVID Mortality	OR 95%CI Hypertension and severe COVID 2.27 (1.80-2.86) I^2=8% Stratified by age: <50 years 2.21 (1.58-3.10) I^2=0% $\geq$50 years 2.32 (1.70-3.17) I^2=42% Hypertension and mortality 3.48 (1.72-7.08) I^2=56%
Zhao, Meng[33] December 2019 to March 22, 2020 N=11 studies (2,002 patients)	Smoking history	Severe COVID	OR (95% CI) Smoking history 1.98 (1.29-3.05) I^2=44%

11 China Case series Methodological index non-randomized studies (MINORS) statement, rangre10-13 (overall quality moderate) AMSTAR2: Critically low quality			
Zheng, Peng[34] January 1, 2020 to Mar 20, 2020 N=13 studies (3,027 patients) 13 China Case-control/cohort MINORS statement, range 18-21 (all low risk) AMSTAR2: Low quality	Current smoking Diabetes mellitus CVD Hypertension	Composite outcome of severe COVID/mortality	OR (95% CI) Current smoking N=5 studies (1,980 patients) 2.04 (1.32-3.25) I^2=0% Diabetes mellitus N=11 studies (2,579 patients) 3.68 (2.68-5.03) I^2=45% CVD N=10 studies (2,422 patients) 5.19 (3.25-8.29) I^2=37% Hypertension N=10 studies (2,527 patients) 2.72 (1.60-4.64) I^2=72%
Zuin, Rigatelli[76] Inception to April 10, 2020 N=9 studies (1,686 patients) Primary study origin NR Primary study design NR Newcastle-Ottawa Scale, 7 high quality AMSTAR2: Low quality	COVID-19 Acute cardiac injury	Acute cardiac injury Mortality	Incidence of acute cardiac injury 24% OR (95% CI) Acute cardiac injury and mortality 21.65 (8.60-54.52) I^2=82%

OR; Odds ratio, RR; Relative risk, SMD; Standardised mean difference, CI; Confidence interval, I^2; I-squared test for heterogeneity, AMSTAR2; a critical appraisal tool for systematic reviews, BMI; Body mass index, CVD; Cardiovascular disease, CAD; Coronary artery disease, CHD; Coronary heart disease, ICU; Intensive care unit, NR; not reported.
N=studies included in meta-analysis (n=patients)
Severe COVID-19 (as described in primary systematic reviews)

Appendix 4. AMSTAR 2 ratings for the included reviews.

Study first and second author	AMSTAR 2 Rating	1		2			3		4			5		6		7			8			9			10		11		12		13		14		15		16	
		Y	N	Y	PY	N	Y	N	Y	PY	N	Y	N	Y	N	Y	PY	N	Y	PY	N	Y	PY	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Aggarwal, Cheruiyot[40]	Low quality		X	X			X			X		X		X			X				X	X				X	X		X			X		X		X		X	
Almeshari, Alobaidi[79]	Low quality	X		X				X		X		X		X				X		X			X			X	X			X			X		X		X		X
Alqahtani, Oyelade[67]	Low quality	X		X			X			X		X		X				X		X		X				X	X			X		X	X			X	X	
Bajgain, Badal[35]	Critically low quality	X				X		X		X			X		X			X			X			X		X	X			X		X		X		X	X	
Barrera, Shekhar[36]	Low quality	X		X			X				X	X		X				X		X		X				X	X		X		X		X		X	X	
Bennett, Tafuro[75]	Low quality	X				X		X		X		X		X				X		X		X				X		NA		NA		X		X		NA	X	
Bhatia, Pedapati[85]	Critically low quality	X				X	X			X		X			X			X			X			X		X		NA		NA		X		X		NA	X	
Biswas, Rahaman[37]	Moderate quality	X				X		X		X		X			X			X		X		X				X	X		X		X			X	X		X	
Chang, Elhusseiny[38]	Moderate quality	X			X			X		X		X		X				X		X		X				X	X		X		X			X	X		X	
Chen, Gong[15]	Low quality	X				X		X		X		X		X				X		X		X				X	X		X			X	X		X		X	
Chidambaram, Tun[41]	Low quality	X		X			X				X	X		X				X	X			X				X	X		X		X		X		X		X	
De Lorenzo, Kasal[16]	Moderate quality	X				X		X		X		X			X			X			X	X				X	X		X		X		X		X		X	
Fang, Li[2]	Moderate quality	X				X		X		X			X	X				X			X		X			X	X		X		X		X		X		X	
Figliozzi, Masci[50]	Moderate quality	X		X			X		X				X		X			X	X				X			X	X		X		X			X	X		X	
Flook, Jackson[86]	Critically low quality	X		X			X			X		X		X				X			X			X		X		NA		NA		X		X		NA	X	
Florez-Perdomo, Serrato-Vargas[68]	Moderate quality	X				X	X		X			X			X			X			X	X				X	X		X		X			X	X		X	
Fridman, Bullrich[80]	Critically low quality	X				X		X		X		X			X			X			X			X		X		X	X		X			X	X		X	
Fu, Wang[17]	Moderate quality	X				X		X	X			X		X				X		X		X			X		X		X		X		X		X		X	

Study first and second author	AMSTAR 2 Rating	1		2			3		4			5		6		7			8			9			10		11		12		13		14		15		16	
		Y	N	Y	PY	N	Y	N	Y	PY	N	Y	N	Y	N	Y	PY	N	Y	PY	N	Y	PY	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Gu, Zhang[77]	Moderate quality	X				X	X			X		X		X				X		X		X				X	X		X		X		X		X		X	
Gulsen, Yigitbas[69]	Moderate quality	X		X			X			X		X		X				X		X		X				X	X		X		X		X		X		X	
Hamam, Goda[81]	Moderate quality	X				X		X		X		X		X				X		X			X			X	X		X		X		X			X	X	
Hammoud, Bendari[82]	Critically low quality	X				X		X		X		X			X			X			X			X		N		NA		NA		X		X		NA	X	
Han, Diao[23]	Critically low quality	X		X			X			X			X	X				X		X			X			X		X		X		X	X		X		X	
Hessami, Shamshirian[51]	Low quality	X			X		X			X		X		X				X		X			X			X		X	X		X			X	X		X	
Hu, Sun[52]	Moderate quality	X				X	X			X			X	X				X			X	X				X	X		X		X		X		X		X	
Islam, Barek[4]	Moderate quality	X				X		X		X		X		X				X			X	X				X	X		X		X			X	X		X	
Izcovich, Ragusa[53]	Low quality	X		X			X		X			X		X				X			X	X				X	X		X			X		X		X	X	
Jain, Yuan[18]	Low quality	X		X			X		X			X		X				X		X		X				X	X			X		X		X		X	X	
Khan, Khan[42]	Low quality	X				X	X		X			X		X				X		X		X				X	X		X			X	X		X		X	
Kumar, Arora, Clinical Features[55]	Critically low quality	X				X	X				X		X		X			X		X		X				X	X			X		X		X		X	X	
Kumar, Arora, Diabetes[54]	Low quality	X		X			X				X	X			X			X		X		X				X	X		X		X		X		X		X	
Li, Guan[19]	Low quality	X				X		X			X	X		X				X		X		X				X	X		X		X		X		X		X	
Li, He[20]	Low quality	X				X	X			X			X	X				X			X	X				X	X		X			X	X			X	X	
Li, Huang[12]	Low quality	X		X			X			X		X			X			X			X	X				X	X		X			X	X		X			X
Liu, Chen[21]	Low quality	X				X		X	X			X		X				X		X		X				X	X		X			X		X	X		X	
Liu, Zhang[70]	Critically low quality	X			X		X			X		X		X				X		X			X			X		X		X		X		X	X		X	
Lu, Zhong[56]	Moderate quality	X		X				X	X			X		X				X			X	X				X	X		X		X		X		X		X	

Study first and second author	AMSTAR 2 Rating	1		2			3		4			5		6		7			8			9			10		11		12		13		14		15		16	
		Y	N	Y	PY	N	Y	N	Y	PY	N	Y	N	Y	N	Y	PY	N	Y	PY	N	Y	PY	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Luo, Fu[1]	Moderate quality	X				X		X	X			X		X				X		X		X				X	X		X		X		X		X			X
Ma, Gu[13]	Low quality	X		X			X				X	X		X				X	X			X				X	X		X		X		X		X		X	
Mantovani, Byrne[64]	Moderate quality	X				X	X			X		X			X			X		X		X				X	X		X		X		X		X		X	
Mao, Lin[57]	Critically low quality	X		X			X				X		X	X				X	X				X			X		X		X		X		X		X		
Matsushita, Ding[59]	Moderate quality	X				X	X			X		X		X				X		X		X				X	X		X		X		X		X			X
Momtazmanesh, Shobeiri[60]	Moderate quality	X				X		X		X		X		X				X	X			X				X	X		X		X			X	X		X	
Moula, Micali[61]	Low quality	X				X		X			X		X		X			X		X		X				X	X		X		X		X		X		X	
Nannoni, de Groot[14]	Critically low quality	X		X			X			X		X			X			X			X			X		X		X		X			X		X	X	
Nasiri, Haddadi[78]	Moderate quality	X				X		X	X			X		X				X			X	X				X	X		X		X			X	X		X	
Noor, Islam[3]	Moderate quality	X				X		X	X			X		X				X			X	X				X	X		X		X			X	X		X	
Palaiodimos, Chamorro-Pareja[65]	Moderate quality	X				X		X		X		X		X				X		X		X				X	X		X		X		X		X		X	
Parohan, Yaghoubi[62]	Critically low quality	X				X		X		X			X	X				X		X		X				X	X		X		X			X	X		X	
Parveen, Sehar[22]	Critically low quality	X				X		X		X		X		X				X			X	X				X	X			X		X		X		X	X	
Patanavanich, Glantz[71]	Moderate quality	X		X			X			X			X	X				X		X		X				X	X		X		X		X		X		X	
Patel, Malik, Shah[72]	Critically low quality	X		X			X				X	X		X				X		X		X				X	X		X		X		X			X	X	
Patel, Malik, Usman[39]	Critically low quality	X		X			X		X			X		X				X		X		X				X		X		X		X	X			X	X	
Porto, Iamonti[24]	Critically low quality	X			X		X				X	X			X			X		X			X			X		X	X		X			X		X	X	
Reddy, Charles[6]	High quality	X		X			X			X		X		X				X	X			X			X		X		X		X		X		X		X	
Rhim, Park[43]	Low quality	X		X			X			X		X			X			X		X		X				X	X			X		X	X		X		X	

Study first and second author	AMSTAR 2 Rating	1		2			3		4			5		6		7			8			9			10		11		12		13		14		15		16	
		Y	N	Y	PY	N	Y	N	Y	PY	N	Y	N	Y	N	Y	PY	N	Y	PY	N	Y	PY	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Roncon, Zuin[66]	Critically low quality	X			X		X				X	X		X				X		X			X			X		X	X		X		X		X		X	
Sabatino, De Rosa[7]	Moderate quality	X		X			X			X		X		X				X	X			X				X	X			X		X		X		X		X	
Sales-Peres, Azevedo-Silva[73]	Critically low quality	X		X			X				X	X			X			X		X			X			X		X	X		X		X		X		X	
Sepandi, Taghdir[25]	Critically low quality	X		X			X				X		X	X				X		X			X			X		X	X		X			X	X		X	
Shafi, Shaikh[83]	Low quality	X			X		X			X		X		X				X		X			X			X		NA		NA		X		X		NA	X	
Shao, Shang[26]	Low quality	X			X		X			X			X		X			X		X			X			X		X	X		X		X		X		X	
Shi, Wang[44]	Low quality	X		X			X			X			X	X				X	X				X			X	X			X		X	X			X		X	
Sinclair, Zhu[84]	Moderate quality	X			X		X			X			X	X				X		X			X			X	X		X		X		X			X	X	
Sreenivasan, Khan[45]	Critically low quality	X			X		X			X		X		X		X			X				X			X		X		X		X		X		X	X	
Ssentongo, Ssentongo[46]	Moderate quality	X		X			X			X		X		X				X	X			X				X	X		X		X		X		X		X	
Tabrizi, Lankarani[47]	Critically low quality	X		X			X				X	X		X				X		X		X				X		X		X		X	X		X		X	
Tamara, Tahapary[11]	Moderate quality	X			X		X			X			X		X			X		X			X			X		NA		NA	X		X			NA	X	
Taylor, Hofmeyr[48]	Critically low quality	X			X		X				X	X		X				X		X			X			X		X		X		X	X			X	X	
Tian, Jiang[49]	Critically low quality	X			X		X			X		X		X				X	X				X			X		X		X		X		X		X		
Villalobos, Ott[63]	Moderate quality	X		X			X			X			X	X				X			X	X				X	X		X		X		X		X		X	
Wang, Deng[27]	Critically low quality	X		X			X				X	X		X				X	X			X				X		X	X		X		X		X		X	
Wang, Li[28]	Critically low quality	X		X			X			X		X		X				X		X			X			X		X		X		X	X		X		X	
Wu, Liu[5]	Moderate quality	X		X			X			X			X	X				X	X			X				X	X		X		X		X		X		X	
Wu, Tang[29]	Moderate quality	X		X			X			X			X		X			X		X			X			X	X		X		X		X		X		X	

Study first and second author	AMSTAR 2 Rating	1		2			3		4			5		6		7			8			9			10		11		12		13		14		15		16	
		Y	N	Y	PY	N	Y	N	Y	PY	N	Y	N	Y	N	Y	PY	N	Y	PY	N	Y	PY	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Wu, Zuo[58]	Critically low quality	X			X		X			X		X		X				X		X		X				X		X		X		X		X		X		X	
Xu, Mao[30]	Critically low quality	X			X		X			X			X	X				X	X				X			X		X		X		X		X		X		X	
Youssef, Hussein[31]	Moderate quality	X		X			X			X		X		X				X		X		X				X	X		X		X		X		X		X	
Yu, Wu[74]	Moderate quality	X		X			X			X		X		X				X		X		X				X	X		X		X		X		X		X	
Zhang, Shen[8]	Moderate quality	X		X			X			X		X			X			X	X			X				X	X		X		X		X		X		X	
Zhang, Wu[32]	Critically low quality	X			X		X				X	X			X			X		X			X			X	X			X		X	X		X		X X	
Zhao, Meng[33]	Critically low quality	X		X			X				X	X		X				X		X			X			X	X			X		X	X		X		X X	
Zheng, Peng[34]	Low quality	X		X			X			X			X	X				X		X			X			X	X			X		X	X			X	X	
Zuin, Rigatelli[76]	Low quality	X		X			X			X		X		X				X		X			X			X	X			X		X	X			X		

NA: not applicable (meta-analysis not performed to score this category)

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