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COVID-19 and its cardiovascular effects: a systematic review of prevalence studies (Review)

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[Prototype Review]

COVID-19 and its cardiovascular effects: a systematic review of prevalence studies

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ABSTRACT

Background

A small minority of people with coronavirus disease 2019 (COVID-19) develop a severe illness, characterised by inflammation, microvascular damage and coagulopathy, potentially leading to myocardial injury, venous thromboembolism (VTE) and arterial occlusive events. People with risk factors for or pre-existing cardiovascular disease may be at greater risk.

Objectives

To assess the prevalence of pre-existing cardiovascular comorbidities associated with suspected or confirmed cases of COVID-19 in a variety of settings, including the community, care homes and hospitals. We also assessed the nature and rate of subsequent cardiovascular complications and clinical events in people with suspected or confirmed COVID-19.

Search methods

We conducted an electronic search from December 2019 to 24 July 2020 in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, covid-19.cochrane.org, ClinicalTrials.gov and EU Clinical Trial Register.

Selection criteria

We included prospective and retrospective cohort studies, controlled before-and-after, case-control and cross-sectional studies, and randomised controlled trials (RCTs). We analysed controlled trials as cohorts, disregarding treatment allocation. We only included peer-reviewed studies with 100 or more participants, and excluded articles not written in English or only published in pre-print servers.

Data collection and analysis

Two review authors independently screened the search results and extracted data. Given substantial variation in study designs, reported outcomes and outcome metrics, we undertook a narrative synthesis of data, without conducting a meta-analysis. We critically appraised all included studies using the Joanna Briggs Institute (JBI) checklist for prevalence studies and the JBI checklist for case series.

Main results

We included 220 studies. Most of the studies originated from China (47.7%) or the USA (20.9%); 9.5% were from Italy. A large proportion of the studies were retrospective (89.5%), but three (1.4%) were RCTs and 20 (9.1%) were prospective.

Using JBI's critical appraisal checklist tool for prevalence studies, 75 studies attained a full score of 9, 57 studies a score of 8, 31 studies a score of 7, 5 studies a score of 6, three studies a score of 5 and one a score of 3; using JBI's checklist tool for case series, 30 studies received a full score of 10, six studies a score of 9, 11 studies a score of 8, and one study a score of 5

We found that hypertension (189 studies, n = 174,414, weighted mean prevalence (WMP): 36.1%), diabetes (197 studies, n = 569,188, WMP: 22.1%) and ischaemic heart disease (94 studies, n = 100,765, WMP: 10.5%) are highly prevalent in people hospitalised with COVID-19, and are associated with an increased risk of death. In those admitted to hospital, biomarkers of cardiac stress or injury are often abnormal, and the incidence of a wide range of cardiovascular complications is substantial, particularly arrhythmias (22 studies, n = 13,115, weighted mean incidence (WMI) 9.3%), heart failure (20 studies, n = 29,317, WMI: 6.8%) and thrombotic complications (VTE: 16 studies, n = 7700, WMI: 7.4%).

Authors' conclusions

This systematic literature review indicates that cardiometabolic comorbidities are common in people who are hospitalised with a COVID-19 infection, and cardiovascular complications are frequent. We plan to update this review and to conduct a formal meta-analysis of outcomes based on a more homogeneous selected subsample of high-certainty studies.

PLAIN LANGUAGE SUMMARY

What type of heart and blood vessel problems complicate COVID-19 infections, how common are they and what other medical conditions do these patients have?

Background

Many people infected by COVID-19 have few or no symptoms. However, COVID-19 can make the blood 'sticky', clogging up both small blood vessels (capillaries) and large ones, which may cause heart attacks, strokes or blood clots in the legs or lungs. These can be fatal. People who have diabetes, high blood pressure or pre-existing heart problems are at greater risk of developing such complications if they get COVID-19.

Our research question

We wanted to find out, in cases of confirmed or suspected COVID-19:

- what are the most common pre-existing heart and blood vessel (cardiovascular) problems (for example, diabetes, high blood pressure and obesity)

- what are the most common complications affecting the heart and blood vessels (for example, irregular heartbeat, blood clots, heart failure and stroke) in different setting (in the community, care homes or in hospital).

What we did

We searched for published studies that reported heart and blood vessel problems in people with possible or confirmed COVID-19. Studies could be of any design and could take place anywhere, but they had to have been checked by other researchers (be peer-reviewed), be written in English, and include at least 100 cases.

The evidence is current until July 2020.

What we found

We found 220 studies that reported relevant information, but the quality of the information was often poor. Studies were mostly from China and the USA. Most studies only had information on the small minority of cases that were admitted to hospital with COVID-19, often to the intensive care unit.

We found that high blood pressure, diabetes and heart disease are very common in people hospitalised with COVID-19 and are associated with an increased risk of death. More than one-third of patients with COVID-19 had a history of high blood pressure, 23.5% had a pre-existing heart or blood vessel problem, 22.1% had diabetes, and 21.6% were obese (many people had more than one of these conditions).

The most common cardiovascular complication in people with COVID-19 was an irregular heartbeat (atrial fibrillation; 8.5%). Blood clots in the legs (6.1%) or lungs (4.3%), and heart failure (6.8%) were also common, but the reported rates may be underestimated because the studies did not always carry out appropriate investigations. Heart attacks (1.7%) and strokes (1.2%) were reported less often. Blood tests also often suggested heart damage or stress.

Next steps

The studies focused on people in hospital, with severe COVID-19, so the results may not apply to people who had milder COVID-19 who were not hospitalised. The studies were very different from each other and did not always report the results in the same way or use the most reliable methods. Accordingly, our confidence in the precision of the prevalence of pre-existing disease and of cardiovascular complications is not high.

We plan to update this review. However, in future, we will focus only on higher-quality evidence to increase the strength of our findings.

BACKGROUND

Many people infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), will have few or no symptoms, but others will develop a severe illness, characterised by widespread inflammation, microvascular damage and coagulopathy (1). The risk of cardiovascular complications is higher in men and in people who have predisposing conditions, such as older age, hypertension, obesity, diabetes and atherosclerosis, which are associated with endothelial dysfunction (2, 3). Inflammation, thrombosis and microvascular obstruction may lead to multi-organ dysfunction, including myocardial injury in both the presence and the absence of atherosclerotic epicardial coronary disease. The cardiovascular presentations of COVID-19 infection are diverse and include thrombosis (arterial, venous and pulmonary), arrhythmias (atrial and ventricular), heart failure and shock. Cardiovascular complications are associated with a high mortality (2-4).

OBJECTIVES

To assess:

- The prevalence of cardiovascular comorbidities of suspected or confirmed COVID-19 in a variety of settings, including the community, care homes and hospitals
- The nature and rate of cardiovascular complications and clinical events in people with suspected or confirmed COVID-19.

METHODS

We reported this systematic review in accordance with the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (5, 256).

Types of studies

We included a range of study designs, including prospective and retrospective cohort studies, controlled before-and-after, case-control and cross-sectional studies, and randomised controlled trials (RCTs) with individual or cluster allocation. We analysed controlled trials as cohorts, disregarding treatment allocation. We only included studies with 100 participants or more.

Excluded studies were

- Not written in English
- Not original research (e.g. reviews, editorials and letters)
- Theses, book chapters or conference abstracts
- Animal or laboratory studies, not carried out in a clinical setting
- Purely epidemiological reports (i.e. only demographics and mortality rate, with no clinical characteristics)
- Case reports and series describing cardiovascular complications
- Pre-print reports (i.e. without or prior to peer review)

Types of participants

People with suspected or confirmed COVID-19 in any setting.

Types of outcome measures

Outcomes of interest are restricted to cardiovascular complications and clinical events:

Arterial

- Myocardial Infarction or acute coronary syndrome
- Stroke
- Peripheral arterial occlusion (including loss of viability of appendages and amputation).

Venous

- Deep venous thrombosis
- Pulmonary thrombo-embolism

Arrhythmias

- Supra-ventricular (including atrial fibrillation)
- Sustained ventricular tachycardia or fibrillation, or both
- Atrioventricular block

Circulatory failure

- Shock
- Ultrafiltration or new onset of dialysis, or both

Myocarditis

- Any mention

Biomarkers

- Raised troponin (above upper reference limit)
- Raised natriuretic peptides (BNP or NT-proBNP)
- Impaired left ventricular systolic function
- Impaired right ventricular systolic function
- QT prolongation

Death

- All-cause

Electronic searches

We searched the following electronic databases on 24 July 2020:

- The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 7 of 12, 2020)
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to July 22, 2020)
- Embase (Ovid, 1980 to 2020 week 29)

A Cochrane Information Specialist drafted a preliminary search strategy for MEDLINE, informed by a content expert and independently peer-reviewed. We then adapted this for the other databases. The search strategies are in Appendix 1. The searches were run with a date limit from 2019, when COVID-19 emerged.

Searching other resources

We also searched the following trials registers for ongoing or unpublished trials on 24 July 2020:

- Cochrane COVID-19 Study Register (covid-19.cochrane.org)
- ClinicalTrials.gov (clinicaltrials.gov)

- EU Clinical Trial Register (clinicaltrialsregister.eu)

Selection of studies

We uploaded all articles retrieved to a reference management database (Covidence) and removed duplicate references.

Two review authors independently conducted screening in two stages; first by title and abstracts, then by full texts. Due to the large number of papers, five authors (KSL, PP, GD, CW, KM) independently reviewed titles and abstracts to determine their eligibility. A second review author checked all excluded records. We resolved any disagreements through discussion amongst review authors or through adjudication by a third review author.

Data extraction and management

Four review authors (KSL, GD, CW, KM) independently extracted and collected study characteristics and information from included studies on to a data-collection template. An independent review author (PP) double-checked for accuracy. We resolved discrepancies by consensus or escalated disagreements to an additional review author.

Where available, we collected the following data:

- Study design, size and country where the research was conducted;
- Setting: home/community, residential care, hospital admissions or intensive care unit (ICU);
- Participant baseline characteristics, including age, sex, ethnicity, smoking history, co-morbidities (such as hypertension, diabetes, ischaemic heart disease (IHD), cardiovascular disease (CVD), cerebrovascular accident (CVA), heart valve disease, congenital heart disease, heart failure, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease (CKD), cancer, obesity), body mass index, cardiac implantable electrical devices (pacemakers or defibrillators);
- Signs and severity: heart rate and rhythm, blood pressure, temperature, respiratory support required, partial pressure of oxygen (pO2);
- Biomarkers: NT-proBNP, BNP, troponin, hsCRP (or CRP), D-dimer, creatinine (or eGFR);
- Echocardiography/electrocardiography (ECG) information (i.e. left ventricular ejection fraction (LVEF), QT);
- Medications such as ACE-I, ARB, ARNI, MRA, beta-blockers, aspirin, oral anticoagulants, P2Y12 inhibitors, statin, diuretic (any, thiazide, loop diuretic).

Assessment of risk of bias and quality in included studies

Four review authors (KSL, GD, CW, and KM) independently assessed the quality of the studies using the Joanna Briggs Institute (JBI) checklist for prevalence studies (6) and the JBI checklist for case series, respectively. In summary, these tools rate the quality of selection, measurement and comparability of studies and give a score for prevalence studies (maximum of 9) and case series (maximum of 10).

Data synthesis

We tabulated outcome results from each study in detail, to enable inspection and assessment of the potential patterns within the data. Given substantial variation in study designs, reported outcomes and outcome metrics, we undertook a narrative synthesis of data, deeming formal quantitative meta-analyses inappropriate. We obtained the weighted mean by adding all the prevalent or incident cases for each study, divided by the total number of the participants included in those cohorts.

RESULTS

Study characteristics

After removing duplicates, we identified 5464 abstracts, of which we assessed 461 as full-text articles for eligibility. We excluded 241 of these, leaving 220 unique publications to be included in our review (Table 1; Table 2; Figure 1) (7-226). Most of the studies originated from China (47.7%) or the USA (20.9%); 9.5% were from Italy. A large proportion of the studies were retrospective (89.5%), but three (1.4%) were randomised controlled trials (RCTs) and 20 (9.1%) were prospective.

Figure 1.

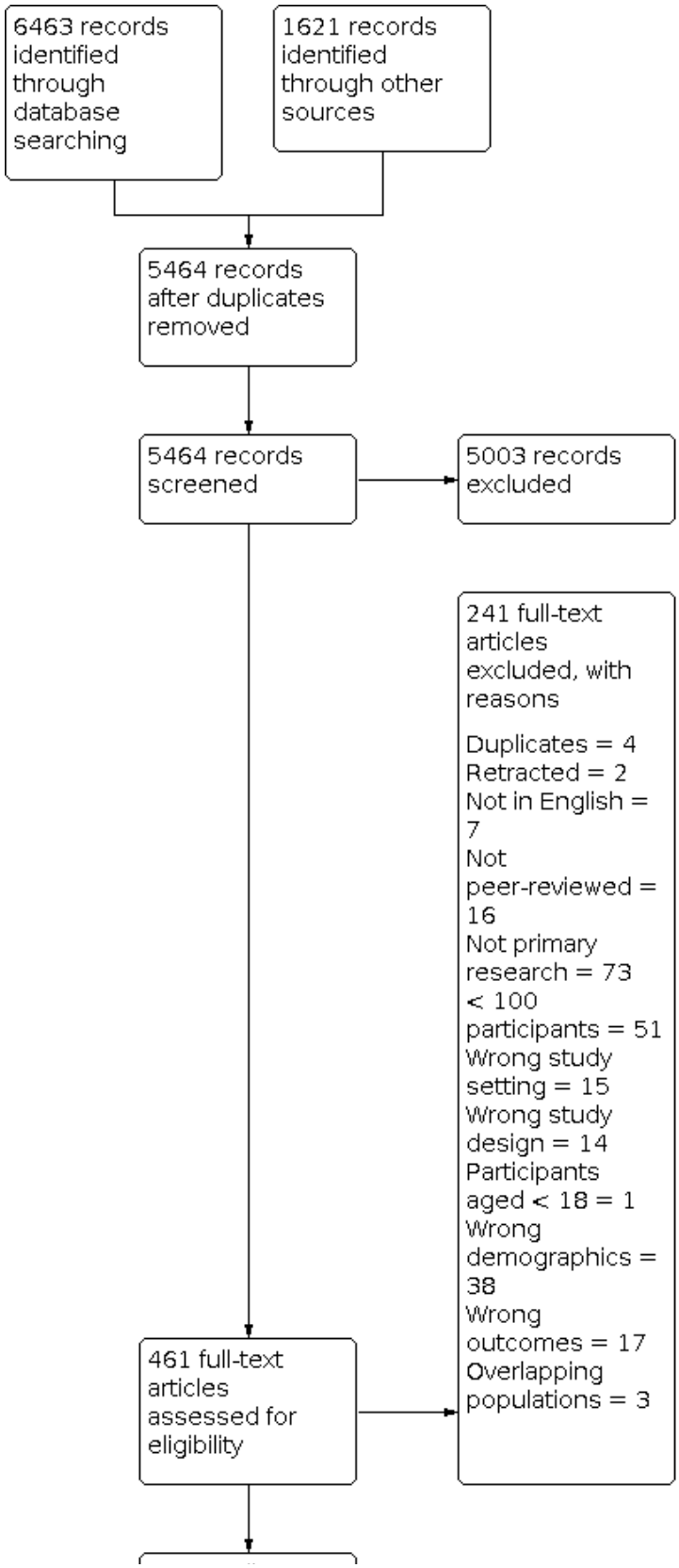
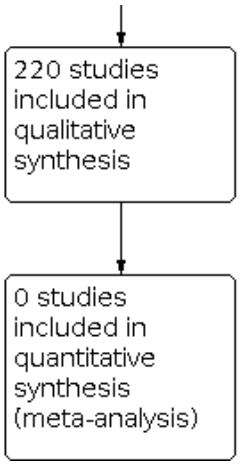


Figure 1. (Continued)



Using JBI's critical appraisal checklist tool for prevalence studies,75 studies attained a full score of 9, 57 studies a score of 8, 31 studies a score of 7, five studies a score of 6, three studies a score of 5 and one a score of 3. Using JBI's checklist tool for case series, 30 studies received a full score of 10, six studies a score of 9, 11 studies a score of 8, and one study a score of 5.

Demographics and cardiovascular comorbidities

The mean or median age of participants included in these studies ranged from ~ 30 to 78 years. Most studies enrolled participants who had been hospitalised. There was a slight predominance of men when participants were enrolled from medical wards, but the proportion increased when participants were enrolled from intensive care units (ICUs). Two studies recruited only women of reproductive age. The weighted mean prevalence (WMP) of pre-existing cardiovascular disease was 23.5% amongst 102 studies that reported this co-morbidity, although the definition of what cardiovascular disease comprised (e.g. hypertension, ischaemic heart disease) was often unclear (Table 1). Hypertension (WMP: 36.1%), type II diabetes (WMP: 22.1%) and ischaemic heart disease (WMP: 10.5%) were commonly-reported cardiovascular comorbidities, and their prevalence increased with age.

Amongst 1,320,488 COVID-19 cases reported in the USA by 30 May 2020 and analysed by the Centre for Disease Control and Prevention (CDCP), the median age was 48 years (30). The incidence of COVID-19 was similar for women and men. Men were more likely than women to be hospitalised (16% versus 12%) or admitted to ICU (3% versus 2%) in the CDCP report. Amongst 287,320 cases reported by CDCP that had information on underlying health conditions, cardiovascular disease (32%) and diabetes (30%) were the most common. The prevalence of CVD was 20.2% in those aged 40 to 49 years, increasing to 60.6% amongst those older than 80 years. The prevalence of diabetes was highest amongst those aged 60 to 79 years (46%).

Obesity (WMP: 21.6%) was common (exceeding 57%) in studies originating from the USA, but was rarely reported in studies from China. Fifty-four studies reported prevalent heart failure (WMP 6.5%). Valve disease was reported less frequently (WMP 3.7%; five studies only).

Cardiovascular complications of COVID-19

Information on the incidence of cardiovascular events was derived almost exclusively from the small proportion of participants infected with COVID-19 who were admitted to hospital. However, there are case reports of acute (fatal) cardiovascular events in the community associated with symptoms of COVID-19 (227). Population-based studies have suggested that fewer people have presented to hospital with acute cardiovascular events during this pandemic; it is unclear whether this reflects a reduction in events, perhaps due to changes in behaviours and lifestyle, or avoidance of seeking medical attention (228). Some publications have described an increase in sudden deaths in the community during the pandemic; presumably very few of these cases coincided with COVID-19 infection (229).

Arterial events

In 16 studies, the WMI of myocardial infarction or acute coronary syndrome in people hospitalised with COVID-19 was 1.7% (range 0% to 3.6%). In 20 studies, the WMI for stroke was 1.2% (range 0% to 9.6%). In a cohort of 219 people hospitalised with COVID-19, 11 (6 men) developed ischaemic (4.6%) or haemorrhagic (0.5%) stroke; their mortality was substantial (54%) (155). In a retrospective study conducted in 844 participants with COVID-19 in the USA, 2.4% had ischaemic stroke and 0.9% an intracranial haemorrhage (85). Amongst 9358 participants with COVID-19 aged under 50 years admitted in different healthcare organisations worldwide (36% in USA), 64 (0.7%) had a stroke. In this study, participants who developed a stroke were more likely to have hypertension (61% versus 12%), diabetes (33% versus 6.5%), obesity (47% versus 17%) and heart failure (16% versus 1.5%) and were also more likely to die (15.6% versus 0.6%) (34). Other peripheral arterial thrombotic complications, such as acute limb or mesenteric ischaemia, were rarely reported (24).

Venous complications

For people hospitalised with COVID-19, the WMI for venous thromboembolism in 16 studies was 7.4% (range 0% to 46.2%) with the WMI of deep vein thrombosis (DVT) and pulmonary embolism (PE) being rather similar (6.1% and 4.3%, respectively). In a cross-sectional study conducted in China, 143 participants admitted with COVID-19 were screened for DVT using compression venous ultrasound; DVT was identified in 46%, but only one participant was diagnosed with pulmonary embolism (25). People with DVT were

more likely to be older, had higher D-dimer and high-sensitivity troponin levels, and a worse prognosis. In a prospective study conducted in 156 participants with COVID-19 and elevated D-dimer (> 1000 ng/mL), Demelo-Rodríguez and colleagues identified asymptomatic DVT in 14.7% participants (23).

A prospective study that enrolled 150 consecutive patients admitted in four ICUs in France showed a high incidence (25%) of pulmonary embolism in 99 of those who underwent a computed tomography pulmonary angiogram (CTPA) (24). Of 184 participants with severe COVID-19 admitted to an ICU in the Netherlands, 14% developed a PE; stroke and venous peripheral thrombotic events were less frequent (1.6% for both) (168). Of 1240 participants with COVID-19 who underwent CTPA in 24 French hospitals, 8.3% had a PE (67). Participants with PE were more likely to be men, less likely to have a history of atrial fibrillation or stroke, less likely to receive treatment with anticoagulants, and had higher D-dimer levels. Those who developed PE were more likely to be transferred to ICU (31% versus 14%). However, in this study, the incidence of PE was not associated with greater mortality. Lower rates of PE (from 0.7% to 6.6%) have been reported in other studies.

Arrhythmias and other ECG abnormalities

Atrial fibrillation was a common comorbidity (WMP 11.1%) but the distinction between the prevalence and incidence of this arrhythmia was not always clear. Amongst admissions for COVID-19, the WMI for supraventricular arrhythmias was 8.5% (range: 0.0% to 24.7%), for ventricular arrhythmias was 2.7% (range 0.0% to 12.4%) and for either or otherwise unspecified arrhythmias the WMI was 9.3% (range 0% to 30.3%). Arrhythmias were more likely to be reported in severely-ill participants, in those with an elevated plasma troponin (173), or in participants receiving interventions for COVID-19 that are known to prolong the QT interval, such as hydroxychloroquine, particularly when given in combination with azithromycin (63). New-onset atrial fibrillation was relatively common in those frequently monitored or admitted to ICU (14% in one study (51) and 8.5% and 8.0% in two other studies (18, 148)). Shao and colleagues reviewed hospital records from 761 people with severe COVID-19 admitted to the Union Hospital in Wuhan, China, and reported that resuscitation was attempted after an in-hospital cardiac arrest in 17.8% of cases. The initial cardiac rhythm was asystole in almost 90%; survival was poor (~ 3% at 30 days) (89). A high rate of cardiac arrest was also reported by Rosenberg and colleagues (12.4%) (63). Ventricular tachycardia or fibrillation has been reported less frequently, in up to 5.9% of hospitalised patients, as reported by Guo and colleagues (167). Development of advanced atrioventricular (AV) block is rare (0.1%) (91). A clinically-important increase in the QT interval was reported in 7.6% (WMI of 10 studies, n = 3989 participants) of those hospitalised with COVID-19; more frequently in those who received hydroxychloroquine, or with renal dysfunction (27). In the study by Saleh and colleagues, that prospectively enrolled 201 participants treated with chloroquine or hydroxychloroquine, 4% had a QTc > 500 ms at baseline, increasing to 9% during treatment; 3.5% of participants required treatment discontinuation due to QT prolongation, but no case of torsades de pointes was reported (18). Treatment with hydroxychloroquine was also discontinued in eight participants (10%) enrolled in another study, due to electrocardiographic modifications, including a QT increase > 60 ms or development of QT > 500 ms (n = 7), and one case of first-degree AV block (172). A QT increase of > 60 ms from baseline was rarer (0.8%) in those enrolled by Million and colleagues in Marseille, France (75).

Circulatory failure

Amongst almost 40,000 patients, predominantly admitted to ICU, the WMI of shock or treatment with vasopressors was 18.0% (range 0.2% to 71.0%). Shock was more likely to develop in men (43). Older age was also a risk factor for developing more severe disease and shock, often associated with a high comorbidity burden (131). Up to 50% of participants with a severe COVID-19 infection developed acute kidney injury. The rate of renal replacement therapy (RRT) varied widely amongst reports (WMI 5.1%; range 0.0% to 50.0%). In a prospective study conducted in two hospitals in New York (17) in critically-ill participants, mostly men (67%) aged more than 60 and with a high prevalence of comorbidities such as hypertension (63%), diabetes (36%), and chronic kidney disease (19%), around a third required RRT. In a multicentre cohort study that enrolled 2215 adults with COVID-19 admitted to ICU at 65 hospitals in USA, development of acute kidney injury was common (43%), with 20% receiving RRT, and this was associated with a high mortality (51). Extracorporeal membrane oxygenation (ECMO) was rarely used (WMI of 1.1%; range 0.0% to 8.1% in 50 studies with 38,471 participants), perhaps reflecting low availability.

Heart failure

Heart failure (HF) was a common co-morbidity (WMP 6.5%). The distinction between prevalent and incident heart failure was not always clear in reported studies, but the WMI at 6.8% (range 0.0% to 24.0%) was higher than for any cardiovascular event other than supraventricular tachycardia. The HF phenotype(s) reported were not described.

Myocarditis

We identified only three studies that reported possible cases of myocarditis complicating severe COVID-19 infection (WMI 2.6%: range 0.0% to 12.5%). In a retrospective study that enrolled 112 participants in Wuhan, myocarditis was suspected in 14 (12.5%) because of elevated serum troponin, echocardiographic (often small pericardial effusions) and electrocardiographic abnormalities (205). Of these participants, four had pre-existing heart failure, one had an MI in the previous week, and one had hypertrophic cardiomyopathy; others had cardiovascular comorbidities, including hypertension and diabetes. Echocardiography did not reveal substantial left ventricular systolic dysfunction (i.e. left ventricular ejection fraction (LVEF) < 40%) in any participant. Gupta and colleagues reported that myocarditis, with or without pericarditis, complicated the course of COVID-19 disease in 0.1% and 2.5%, respectively, of 2215 patients admitted to ICU at 65 hospitals in the USA between 04 March and 04 April 2020 (51). Saleh reports a possible case of myocarditis in one out of 210 participants (0.5%) enrolled (18).

Biomarkers

Troponin and natriuretic peptides

When measured, laboratory biomarkers were often deranged. Serum troponin was reported in 90 studies, and was elevated in up to 74% of participants in whom a test was requested. There was a gross heterogeneity in assays used, time of testing and ranges for normality. Cardiac injury was reported in 48 studies and usually

defined as a serum troponin concentration above a reference range or the 99th percentile upper reference limit, with or without new abnormalities at echocardiography or electrocardiography. The incidence of cardiac injury ranged from 4.8%, in a study that enrolled participants older than 60 years with a mild COVID-19 infection (overall mortality 2.9%, (220)), to 54% in critically-ill participants (mortality 41% to 72%). In a prospective study that enrolled 2729 inpatients with COVID-19 in the USA, Petrilli and colleagues showed that critically-ill participants (n = 990) had higher blood concentrations of troponin-I than those with milder disease (n = 1739) (0.07 (0.01 - 0.10) versus 0.02 (0.01 - 0.10) ng/mL) (10). In a retrospective study that enrolled 2736 hospitalised participants in New York (median age 66 years, 60% men, 39% with hypertension (HTN), 26% with type 2 diabetes mellitus (T2DM) and 17% with ischaemic heart disease (IHD)), troponin-I was mildly elevated (> 0.03 to 0.09 ng/dL) in 16.6% and substantially elevated (> 0.09 ng/dL) in 19.4%; increases in troponin were associated with a higher mortality (47). Si and colleagues also found that in-hospital mortality was higher in those with elevated cardiac troponin-I compared to those with normal concentrations (71% (121/170) versus 6.6% (65/984)) (173).

When measured, plasma natriuretic peptides were also often abnormal (i.e. median NT-proBNP was usually > 125 ng/L); plasma concentrations increased with the severity of COVID-19 (139) or the presence of cardiovascular comorbidities. In a prospective study, which enrolled 143 participants hospitalised with COVID-19 (mean age 63 years, 52% men, 39% with HTN, 12% with IHD), BNP was substantially elevated (i.e. > 100 ng/L) in almost 25% of the cohort (median 50 (25 - 99) pg/mL) (25).

However, in studies that enrolled younger participants with few cardiovascular comorbidities, cardiac biomarkers were rarely elevated. For instance, in a study of 158 pregnant women, most of whom were asymptomatic or with mild disease (78%), elevated troponin (> 14 ng/L) was reported in only one case (178).

Other biomarkers: cardiac function at imaging

In a retrospective study of 110 participants hospitalised with COVID-19 who had a transthoracic echocardiogram, Sud and colleagues reported a high prevalence of left ventricular (LV) systolic dysfunction: 54% amongst those who had biomarkers suggesting cardiac injury (n = 24, 22%) and 25% amongst those who did not; 25% also had impaired right ventricular (RV) function (208). Rath and colleagues prospectively enrolled 123 participants hospitalised with a COVID-19 infection, 98 of whom had an echocardiogram: 10.8% had an impaired LVEF (≤ 50%) and 13.7% impaired RV function (26). Of 125 participants (mean age 64 years, 60% with HTN and 41% with T2DM) enrolled in another study (198), 28 (22%) had LVEF < 50% and 16 (14%) had regional wall motion abnormalities which were pre-existent in only six. At follow-up echocardiography, cardiac dysfunction resolved in 82% of these cases.

Death

The overall WMI for mortality was 6.1% (range 0.0% to 100%), increasing to 32% amongst cohorts entirely enrolled in ICU. An analysis of medical notes from 3032 people who died following a COVID-19 infection (9.8% of all COVID-19 related deaths) in Italy, showed that hypertension (68%), type II diabetes (30%) and ischaemic heart disease (28%) were the most prevalent comorbidities, and that dyspnoea was the most common symptom. Fewer than 9% were younger than 65 years and, of these, only 10.9% had no comorbidities. Hospitalisation was complicated by acute renal injury in 22% and by cardiac injury in 11% (44). Chen and colleagues reported clinical characteristics and laboratory findings of 113 participants (out of 799 admitted, 14%) with at least moderate COVID-19 disease who died in Wuhan, China (138). Compared to those who recovered (n = 161), those who died were older (median age: 68 (62 - 77) versus 51 (37 - 66) years), more likely to have hypertension (48% versus 24%), diabetes (21% versus 14%) and cardiovascular disease (14% versus 4%), and to report dyspnoea (62%). They also had higher blood concentrations of NT-proBNP (800 (390 - 1818) vs 72 (20 - 185) pg/mL) and high-sensitivity troponin-I (40.8 (14.7 - 157.8) versus 3.3 (1.9 - 7.0) pg/mL). Cardiovascular complications often preceded death compared to those that survived (heart failure: 49% versus 3%; acute cardiac injury: 77% versus 17%; shock 41% versus 0%).

DISCUSSION

We found that hypertension, diabetes and ischaemic heart disease are common in people hospitalised with COVID-19, and are associated with an increased risk of disease progression and death. In those admitted to hospital, biomarkers of cardiac stress or injury, and inflammation are often abnormal, and the incidence of a wide range of cardiovascular complications is substantial, particularly arrhythmias, heart failure and thrombotic complications. However, it is likely that biases in case-ascertainment and failure to distinguish accurately between pre-existing and incident conditions such as atrial fibrillation and heart failure, leads to over-estimates of the incidence rates of some conditions. The rate of these conditions is higher in people aged over 75 years than in younger people infected with COVID-19, and much lower in people who do not require admission to hospital with perhaps the exception of residents in care homes who may have high rates of morbidity and mortality despite not being admitted to hospital. More information on cardiovascular complications in this group of people is desirable, but may be difficult to obtain (230).

Our results support findings from other published systematic review and meta-analyses that describe a high rate of incident cardiovascular complications in people with severe COVID-19 infection. For instance, Liao and colleagues (231) report incident rates for atrial fibrillation (8.2%) and for ventricular fibrillation or tachycardia (3.3%) similar to our findings. Compared with us, Jimenez and colleagues (232) report a numerically higher incidence of PE (7.1%) and DVT (12.1%), which might reflect a different study design, as they included many studies with fewer than 100 participants. More recently, Fu and colleagues (233) found that, amongst the 6130 hospitalised patients with COVID-19 included in their meta-analysis, the rate of cardiac injury is substantial, exceeding 20%, as also reported by us.

There are many potential mechanisms linking severe COVID-19 infection with cardiovascular complications and poor outcomes. Indeed, for most people dying in hospital of any disease, the terminal event will be associated with the cessation of circulatory function; many deaths can simultaneously be considered as both cardiac and multi-organ.

SARS-CoV-2 enters cells by binding to angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the endothelium of every organ including the lungs, heart and kidney, and might,

in theory, cause direct multi-organ injury (2). Whether there is a specific myocarditis associated with COVID-19 remains uncertain and, if so, whether the incidence differs from other acute systemic viral infections, such as influenza (230). A recent pathology study suggests increased myocardial macrophage infiltration, but is biased by small number of cases where specialist cardiac post-mortem histopathological investigations were performed (234). However, there is strong evidence to suggest that COVID-19 causes a coagulopathy leading to micro- and macro-vascular thrombosis that may account for injury to the lung, heart, kidney and brain (235-237). Prospective clinical studies of disease mechanisms are ongoing (238).

A severe inflammatory illness might destabilise pre-existing cardiovascular disease, particularly in the elderly, who have less cardiovascular reserve. Hypoxia, caused by acute respiratory distress, reduces myocardial oxygen delivery, which may cause myocardial injury and ischaemia, especially in those with underlying ischaemic heart disease. Obesity complicates respiratory function, by increasing chest muscle work and diminishing lung compliance, which might contribute to developing a more severe COVID-19 infection. Diabetes and obesity are also pro-inflammatory conditions that may impair immune system function, and therefore either weaken clearance of pathogens or increase susceptibility to infections (239). Development of hypo- or hyper-glycaemia and ketoacidosis might also contribute to poorer outcomes following a COVID-19 infection amongst those with diabetes.

Infection, inflammation, hyper-coagulability and vascular occlusion are a pathological chain leading to cardiovascular events, particularly in people who are critically ill (240, 241). COVID-19 might cause coronary spasm, plaque rupture, and/or endothelitis with thrombosis and microvascular obstruction leading to myocardial damage, exacerbated by the increasing myocardial demand imposed by the metabolic stress of infection, combined with reduced oxygen supply due to hypoxia and jeopardised blood flow due to hypotension and shock (2, 230, 238). The right ventricle may also be impaired secondarily due to high pulmonary vascular resistance and pulmonary hypertension. Prolonged immobilisation increases the risk of venous thrombosis. The high risk of arterial and venous thromboembolism has led many to advocate therapeutic anticoagulation in severely-ill people with COVID-19, and potentially in earlier stages of the disease where D-dimer or other biomarkers of thrombosis are substantially elevated, although evidence from randomised trials is lacking; therapeutic anticoagulation may increase the risk of bleeding, including cerebral haemorrhage. Trials of both efficacy and safety are required.

The high incidence of atrial arrhythmias reported in people with a severe COVID-19 disease might further increase the risk of thromboembolic events. Atrial and ventricular arrhythmias can be triggered by the metabolic stress of infection, acute myocardial injury, hypoxia, pulmonary hypertension, or heart failure, or may develop as a consequence of medications such as hydroxychloroquine and azithromycin known to cause electrical instability and prolong the QT interval (242). Development of renal dysfunction predisposes to electrolyte abnormalities, arrhythmias and iatrogenic side effects, and further worsens prognosis.

Increases in biomarkers of cardiac injury and stress, such as troponin and natriuretic peptides, may reflect underlying cardiovascular risk factors and disease, rather than being a consequence of direct viral myocardial damage. However, their progressive rise during hospitalisation identifies people with a higher mortality (243). In children with severe COVID-19 infection, coronary artery dilatation, arrhythmias, cardiac dysfunction and elevated blood troponin concentrations have been reported, albeit infrequently, suggesting direct involvement of the heart (244). For adults, imaging of the heart during hospitalisation usually shows little or no reduction in LV systolic function, particularly if troponin is normal. Moreover, histological evidence of the presence of SARS-CoV-2 within the myocardium has rarely been reported, despite several millions of people infected by COVID-19 worldwide so far (245, 246).

We do not yet have strong evidence that the rate of cardiovascular complications observed in people with a severe COVID-19 infection is higher than that reported in similarly-ill people with other infections. For instance, in a cohort of 262 people with severe sepsis who were mechanically ventilated, Landesberg and colleagues found that LV systolic (LVEF ≤ 50%) and diastolic dysfunction (e' < 8 cm/s) were common (23% and 50%, respectively) and associated with high plasma NT-proBNP (5762 (1001 - 15,962 pg/mL)), hs-troponin-T (0.07 (0.02 - 0.17 ng/mL)) and a high mortality (247).

Thrombotic events are also common in people with infections other than COVID-19. In a prospective, multicentre study of 113 participants with severe sepsis, 84% of whom received anticoagulants, 42 (37%) developed venous thromboembolism (VTE), including 3.5% who had a PE (248). Sepsis may also increase the risk of stroke: in an analysis of 121,947 adults admitted with sepsis in California in 2009, 0.5% developed a stroke within a year of hospitalisation (249). In a population-based study of 4389 people with bacteraemia in Denmark, Dalager-Pedersen and colleagues showed that the risk of stroke or acute myocardial infarction (incidence: 3.6%) within a year from hospitalisation was twice as great as that for hospitalised matched controls (incidence: 1.7%) and around 20 times higher than that of the general population (incidence: 0.2%) (250). Up to 85% of people admitted to ICU with a community-acquired pneumonia have, or will develop, an elevated serum troponin (251, 252). Severe sepsis is also associated with a high risk of atrial and fatal or non-fatal ventricular arrhythmias, or development of heart failure (253-255). Although it seems likely that COVID-19 is associated with a greater risk of cardiovascular problems, the risk associated with other serious infections is not trivial.

Strengths and limitations

We included peer-reviewed studies irrespective of their design, but not articles on pre-print servers that might have contained additional information. We only included studies with 100 or more participants, to reduce reporting bias that is more likely in smaller studies. However, most studies were retrospective and therefore highly prone to reporting bias. Most studies comprised hospital cohorts, often focusing on participants admitted to an ICU. Most studies were from China or the USA, so generalisability might therefore be limited. Also, we cannot exclude overlap amongst some reports. We found great heterogeneity in study design, terminology, definitions, and presentation of findings, including reporting of blood tests and length of follow-up, which made data extraction and summary challenging. Accordingly, we decided not to conduct a meta-analysis, but rather mapped the existing literature and summarised our findings in a narrative fashion. We

feel that this approach will inform readers and guide the design and selection of relevant outcomes in future versions of this review. We plan to report a formal meta-analysis of outcomes based on a more homogeneous selected subsample (such as prospective cohort studies (238)) of included studies.

AUTHORS' CONCLUSIONS

This systematic literature review indicates that cardiometabolic comorbidities are common in people who are hospitalised with a severe COVID-19 infection. The most frequent cardiovascular complications are cardiac arrhythmias, heart failure and arterial and venous occlusive events. Laboratory biomarkers may help identify those at greater risk of developing cardiovascular complications and of death.

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Charlene Bridges (Cochrane Heart Information Specialist) developed a draft search strategy and conducted the electronic search. The search strategy was independently peer-reviewed by Robin Featherstone.

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ADDITIONAL TABLES

Table 1. Prevalence of comorbidities and incidence of cardiovascular events

Outcomes	Studies not providing data	Population[a]	Studies providing data[b]	Population	Weighted mean	Range
Prevalence of comorbidities						
Hypertension	31	403,873	189	174,414	36.1%	4.5% to 100%
Obesity	175	492,430	45	85,857	21.6%	0.2% to 57.6%
Diabetes	23	9,099	197	569,188	22.1%	0.0% to 100%
IHD	126	477,522	94	100,765	10.5%	1.0% to 28.2%
CVD	118	117,191	102	461,096	23.5%	0.7% to 68.7%
Heart failure	166	493,386	54	84,391	6.5%	0.0% to 28.0%
CVA	142	510,271	78	68,016	5.1%	0.5% to 19.6%
AF	194	555,913	26	22,374	11.1%	1.0% to 22.8%
Valve disease	215	576,030	5	2257	3.7%	1.8% to 6.8%
Incidence of cardiovascular events						
MI/ACS	204	1,597,182	16	14,273	1.7%	0.0% to 3.6%
Stroke	200	1,588,720	20	22,735	1.2%	0.0% to 9.6%
Heart failure	200	1,582,138	20	29,317	6.8%	0.0% to 24.0%
VTE	204	1,603,755	16	7700	7.4%	0.0% to 46.2%

Table 1. Prevalence of comorbidities and incidence of cardiovascular events *(Continued)*

DVT	205	1,605,127	15	6328	6.1%	0.0% to 46.2%
PE	202	1,604,122	18	7333	4.3%	0.0% to 23.8%
Coagulopathy	203	1,595,440	17	16,015	8.0%	0.5% to 38.0%
Arrhythmia	198	1,598,340	22	13,115	9.3%	0.0% to 30.3%
Supra-ventricular	210	1,605,496	10	5959	8.5%	0.0% to 24.7%
Ventricular	200	1,596,365	20	15,090	2.7%	0.0% to 12.4%
AV-block	217	1,609,826	3	1629	1.3%	0.0% to 2.6%
Prolonging QT	210	1,607,466	10	3989	7.6%	0.0% to 20.0%
Incidence of cardiovascular events (cohorts enrolled predominantly in ICU)						
Shock	181	1,591,125	39	20,330	17.1%	0.2% to 67.0%
Vasopressor support	200	1,590,068	20	21,387	20.9%	3.0% to 71.0%
Shock or vasopressor support	168	1,573,543	52	37,912	18.0%	0.2% to 71.0%
RRT	173	1,572,302	47	39,153	5.1%	0.0% to 50.0%
ECMO	170	1,572,984	50	38,471	1.1%	0.0% to 8.1%
Incidence of cardiovascular events based on cardiac biomarkers and imaging						
Myocarditis	216	1,608,769	4	2686	2.6%	0.0% to 12.5%
Cardiac injury	173	1,583,677	47	27,778	27.6%	0.6% to 100%
LV dysfunction	215	1,610,785	5	670	13%	4.0% to 30.0%
RV dysfunction	216	1,610,910	4	545	14.2%	3.6% to 25.0%
All-cause mortality						
All studies	15	7822	205	1,603,633	6.1%	0.0% to 100%
ICU cohorts only	NA		12	6076	32.0%	8.7% to 72%

[a]A large study (n = 1,320,488) reported comorbidities only for a subset of participants (n = 287,320).
[b]includes studies reporting zero events.
Abbreviations used: ACS – Acute coronary syndrome; AF – atrial fibrillation; AV – atrioventricular; CVD – cardiovascular disease; CVA – cerebrovascular accident; DVT – deep vein thrombosis; ECMO – extracorporeal membrane oxygenation; ; ICU – intensive care unit; IHD – ischaemic heart disease; LV – left ventricular; MI – myocardial infarction; PE – pulmonary embolism; RRT - renal replacement therapy; RV – right ventricular; VTE – venous thromboembolism;

Table 2. Key findings of the 220 studies included in the review

Author	Setting	Country	Participants (No.)	Men (%)	Key findings
Randomised controlled trials (in order of size)					
Wang (7)	H: 100%	China	236	59	• Median age: 65 years; 43% had HTN, 23.7% T2DM and 7% IHD • 0.4% developed ACS, 0.8% DVT, 0.8% PE, and 0.4% a ventricular arrhythmia • 6.3% developed heart failure, 2.5% required RRT • 13.6% died
Cao (8)	H: 100%	China	199	60	• Median age: 58 years; 11.6% had T2DM, 6.5% CVA • 0.5% developed QT prolongation, 4.5% AKI, 0.5% HF; 22% required therapy with vasopressors, and 2% ECMO. 16% were intubated • Mortality: 22%
Deftereos (9)	H: 100%	Greece	105	58	• Median age: 64 years; 44% had HTN, 20% T2DM, 13% IHD, 10% AF • 5.7% required invasive mechanical ventilation • 4.8% died
Prospective studies (in order of size)					
Petrilli (10)	H: 51.9% ICU: 18.7%	USA	5279	49.5	• Median age: 54 years; 43% had HTN, 23% had T2DM, 13% IHD, 7% HF • Critical patients had higher Trop-I than those non-critical (0.07 (0.01 - 0.10) vs 0.02 (0.01 - 0.10) ng/mL) • In-hospital mortality: > 24%. Age, HF and trop-I > 0.1ug/L predicted poorer outcomes
Cen (11)	H: 100%	China	1007	49	• Median age: 61 years; 27% had HTN, 12% T2DM, 6.5% IHD • D-Dimer > 0.5 mg/L: 68% • Mortality: 4.2%. Age, male sex, T2DM and IHD predicted disease progression
Lee (12)	H: 88% ICU: 7%	UK	800	56	• Patients with active cancers • Median age: 69 years; 31% had HTN, 16% T2DM and 14% CVD • Mortality: 28%. Advanced age and CV comorbidities predicted poorer outcomes
Wendel Garcia (13)	H: 100% ICU: 100%	Europe	639	75	• Median age: 63 years; 44% had HTN, 23% T2DM, 13% IHD • D-dimer (1329 (800 - 2813) ug/L) levels often elevated • 23% developed shock, 28.6% AKI, 5.8 cardiac injury; 2.8% required ECMO

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• Mortality: 24.3%. Increasing D-dimer predicted death
Ciceri (14)	H: 100% ICU: 17%	Italy	410	73	• Median age: 65 years; 50% had HTN, 17% T2DM, and 13%IHD • When requested, NT-proBNP (205 (88 - 780) pg/mL) and D-dimer (1.54 (0.84 - 3.28) ug/mL) were often elevated • Mortality: > 23%
Saluja (15)	H: 100% ICU: 1.9%	India	406	65	• Mean age: 36 years, mortality was 1.9% • Age ≥ 60 years was associated with adverse outcomes
Ortiz-Brizuela (16)	H: 45% ICU: 9.3%	Mexico	309	59	• Median age:43 years; 20% had HTN, 13% T2DM, 3% CVD, 40% obesity • Compared to those not admitted to ICU, those admitted to ICU had higher HsTrop-I (10.6 (5.6 - 16.5) vs 4.0 (2.8 - 5.5) pg/ml) • Mortality: 1.6%
Cummings (17)	H: 100% ICU: 100%	USA	257	67	• Median age: 62 years; 63% had HTN, 36% had T2DM, 19% CVD • HsTrop-T (19 (9 - 52) ng/L) and D-dimer (1.6 (0.9 - 3.5) µg/mL) levels were frequently elevated. • Mortality: 39%
Saleh (18)	H: 100%	USA	201	57	• Mean age: 59 years; 60% had HTN, 32% T2DM, 11% IHD, 7.5% HF • At baseline, 4% had prolonged QTc (> 500 ms); 9.4% had QTc > 500 in-hospital • 8% developed AF, 3.9% a ventricular arrhythmia; • Mortality: 2%
Garassino (19)	H: 76% ICU: 7%	8 countries	200	70	• Participants with thoracic cancers • Median age: 68 years; 47% had HTN, 15% T2DM, 15% IHD, 24% smokers • 2% developed an arrhythmia, 1% HF. Mortality: 33%
Rieder (20)	H: 100% ICU: 9.5%	Germany	190	53	• Mean age: 60 years • 4.2% developed VTE, 1% PE. Mortality: 5.3%
Du (21)	H: 100%	China	179	54	• Median age: 58 years; 32% had HTN, 18% T2DM, 16% CVD • Median BNP (645.0 (110.0 - 1504.0) pg/ml) was elevated; ~ 30% trop-I ≤ 0.05 ng/mL • Mortality: 11.7%; elevated troponin predicted outcome
Dubois-Silva (22)	H: 100%	Spain	171	NR	• 4.7% developed a PE

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Demelo-Rodríguez (23)	H: 100% ICU: 10.2%	Spain	156	65	• Screening of participants with D-dimer > 1000 ng/ml • Mean age: 67 years; cancer: 10% • 14.7% had asymptomatic DVT
Helms (24)	H: 100% ICU: 100%	France	150	81	• Mean age: 63 years; 20% had T2DM and 48% CVD • 1.3% developed stroke, 18% VTE (16.7% a PE) • Mortality: 8.7%
Zhang (25)	H: 100% ICU: 10.5%	China	143	52	• Mean age: 63 years; 39% had HTN, 18% T2DM, 12% IHD • BNP (49.9 (24.5-99.0) pg/mL) and HsTrop-I (25% > 26.5 ng/L) were often elevated • 46% developed DVT (PE: 0.7%); • Mortality: 22.4%
Rath (26)	H: 100% ICU: 45%	Germany	123	63	• Mean age: 68 years; 70% had HTN, 24% T2DM, 23% IHD, 20% obese • Median NT-proBNP was elevated (445 (139 - 2714) ng/L), 70% SR at ECG • Mean LVEF: 57(8)%; LVEF was impaired in 10.8%, RVEF in 13.7% • Mortality: 13%
Moschini (27)	H: 100%	Italy	113	75	• Median age: 68 years; 28% had HTN, 14% T2DM, 11% IHD • 1.8% had a ventricular arrhythmia, 21% developed QT > 500 ms • Mortality: 8%
Wei (28)	H: 100% ICU: 30%	China	101	54	• Mean age: 49 years, 21% had HTN, 14%T2DM, 5% IHD • 5% required vasopressors, 15.8% developed cardiac injury • 3% died
Toniati (29)	H: 100% ICU: 43%	Italy	100	88	• Median age: 62 years; 46% had HTN, 17% T2DM, 16% CVD; 31% obese • Trop T (18 (13 - 21) ng/L) and D-Dimer (525 (283 - 1100) ng/mL) were often elevated • Mortality: 20%
Retrospective studies (in order of size)					
Stokes (30)	H: 14% ICU: 2.3%	USA	1,320,488	51	• Median age: 48 years • Of the 287,320 with detailed information: 30.2% had T2DM, 32.2% CVD • Mortality: 5.4%
Ellington (31)	H: 8.1% ICU: 0.95%	USA	91,412	0	• Women aged 15 - 44 years; 2.3% had T2DM, 2.6% CVD; 9% were pregnant • 0.3% required invasive mechanical ventilation

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• 0.2% died
Kammar-García (32)	H: 38% ICU: 4.4%	Mexico	13,842	58	• Mean age: 46 years; 21% had HTN, 18% T2DM, 3% CVD • Mortality: 9.4%
Soares (33)	H: 10.8% Community: 89.2%	Brazil	10,713	45	• 81% were younger than 60 years; 10% had T2DM, 24% CVD • Mortality: 7.7%; risk increased with age
Annie (34)	H: 33.2%	USA (36%) Worldwide	9358	40	• Young participants (median age 38 years); 12% had HTN, 6.5% T2DM, 1.6% HF • 0.7% developed a stroke. • Mortality was 0.7% (15.6% in those with a stroke)
Kuno (35)	H: 54%	USA	8438	54	• Median age: 59 years; 28% had HTN, 19% T2DM, 9% IHD, 7% HF • When measured (n = 5320), troponin was often elevated (43%; 15% < 50years, 71% > 80 years) • Mortality: 14.8%
Mikami (36)	H: 57% OP: 43%	USA	6493	54	• Median age: 59 years; 25% had HTN, 18% T2DM, 8.1% CKD, 6.4% obesity • Elevated troponin (> 0.03 ng/dL): 49.8%; elevated D-dimer (> 2 ug/mL): 40% • Mortality: 13.2%. Elevated troponin and D-dimer increased risk
Qin (37)	H: 100%	China	6033	47	• Median age: 56 years; 25% had HTN, 11.1% T2DM, 5.1% IHD • 14.2% had elevated natriuretic peptides, 6.5% elevated troponin • 8.5% developed HF, 2.2% AKI; • 5% died
Richardson (38)	H: 100% ICU: 6.5%	USA	5700	60	• Median age: 63 years; 56.6% had HTN, 33.8% T2DM, 7% HF • When measured, BNP (385 (106- 1997) pg/mL) and troponin (22.6%) were elevated • QT was prolonged in 6.1% • 9.7% died
Hirsch (39)	H: 100% ICU: 25.6%	USA	5549	61	• Median age: 64 years, 56% had HTN, 33% T2DM, 11% IHD, 27% obesity • 21% developed shock, 36.6% AKI, 5.2% required renal dialysis; • 16.3% died
Jung (40)	H: 38%	Korea	5179	44	• Mean age: 44 years, 22% had HTN, 17% T2DM, 1% IHD, 4% HF • 3% developed an MI, 1% had a cardiac arrest, 7% HF • 4% died

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Fosbøl (41)	H: 49.6%	Denmark	4480	48	• Median age: ~ 55 years, 19% had HTN, 9% T2DM, 8% IHD, 5% HF,9% CVA, 7% AF • Mortality: 10.6%
Price-Haywood (42)	H: 39.7% ICU: 13.6%	USA	3481	40	• 70% black; mean age: 54 years; 31% had HTN, 16% T2DM, 4.4% IHD • BNP (> 100 ng/L) and trop-I (> 0.06 ng/L) elevated in 19.2% and 19.5% respectively • Of those hospitalised, 0.1% developed HF • 23% died
Chen (43)	H: 100% ICU: 31%	China	3309	50	• Median age: 62 years; 30% had HTN, 14% T2DM, 7% CVD • NT-proBNP (138 (49 - 517.5) pg/ml) levels frequently elevated • 47.8% developed shock, 12% AKI, 31% cardiac injury, 19% HF • 9.3% died
Palmieri (44)	H: 100%	Italy	3032	77	• Deceased participants with COVID-19 • 87.9% > 65 years; HTN (68%), T2DM (30%), IHD (28%), HF (16%), AF (22.5%) and CKD (20%) were common CV comorbidities • 21.8% developed AKI, 10.7% cardiac injury
Rastad (45)	H: 100%	Iran	2957	54	• Mean age: 55 years; 9% had T2DM and 10.6% CVD • Mortality: 10.2%; T2DM predicted poorer outcomes
Gao (46)	H: 100%	China	2877	51	• Mean age: 58 years, 30% had HTN, 13% T2DM, 3% IHD • Participants with HTN had higher BNP (11.73 (0.01 - 50.09) vs 0.01 (0.01-24.13) mg/L, P < 0.001) and Trop-I (0.01 (0.01 - 0.02) vs 0.01 (0.01 - 0.01) ng/mL, P = 0.03) than those without HTN • Mortality: 1.9%
Lala (47)	H: 100%	USA	2736	59.6	• Median age: 66 years; 39% had HTN, 26 T2DM, 16.6% IHD, 10% HF, 7.5% AF • Trop-I > 0.09 ng/dL: 19.3%; D-dimer > 1 ug/mL: 66% • Mortality: 18.5%; risk increased with elevated troponin
Kim (48)	H: 100% ICU: 32%	USA	2491	53	• Median age: 62 years; 57% had HTN, 33% T2DM, 34.6% CVD 11.4% HF • 1.5% developed a MI, 2.1% HF, 18.4% AKI, and 15% required vasopressor support • Mortality: 17%; risk increased with advanced age, T2DM and CVD
Phipps (49)	H: 95% ICU: 23%	USA	2273	57	• Median age: 65 years, 60% had HTN, 39%T2DM

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• Peak Hs-Trop: 25 (10 - 79) ng/L, D-dimer 2.5 (1.0 - 10.8) ug/mL • 23% died
Borobia (50)	H: 100% ICU: 10.6%	Spain	2226	48	• Median age: 61 years; 41% had HTN, 17% T2DM, 19% CVD, 11% obesity • 2.1% developed an arrhythmia, 7.8% AKI, 2.3% HF • 20.7% died
Gupta (51)	H: 100% ICU: 100%	USA	2215	65	• Median age: 61 years; 60% had HTN, 39% had T2DM, 13% IHD, 9% HF • Elevated D-dimer (1190 (690 - 2700) ng/mL) • 0.7% developed a stroke, 8.6% VTE (PE: 2.3%), 17.4% an arrhythmia (ventricular: 3.4%), 2.6% a myocarditis, with or without a pericarditis (0.3%), 3.9% HF • 35.4% died
Sousa (52)	H: 11.4% ICU: 5.4%	Brazil	2070	49	• Median age: 44 years; 5.5% had T2DM, 7.3% CVD • Mortality: 6.3%. Old age and CVD increased risk
Wu (53)	H: 100% ICU: 16.8%	China	2041	49	• Median age: 62 years; 27% had HTN, 13% T2DM • Mortality: 9.5%
Merkler (54)	H: 100% ICU: 24.7%	USA	1916	57	• Median age: 64 years; 62% had HTN, 43% T2DM, 26% IHD • 1.6% developed a stroke • Mortality: 14.3% (32% in those with a stroke)
Qin (55)	H: 100%	China	1875	50	• Median age: 63 years, 34% had HTN, 16% T2DM, 10% CVD • NT-proBNP frequently elevated (124 (46-390) pg/mL) • Mortality: 8.5%
Mehta (56)	H: 24% ICU: 9.3%	USA	1735	50	• Mean age: 55 years, 39% had HTN, 19% T2DM, 9% IHD, 8% HF and 26% obesity • 6.4% required mechanical ventilation • 2.5% died
Hernández-Fernández (57)	H: 100%	Spain	1683	NR	• 17 participants had cerebral ischaemia, 5 an intracerebral haemorrhage (1.4%) • Of those with a stroke, 35.7% died
Bravi (58)	H: 41% ICU: 11.9% Community: 59%	Italy	1603	47	• Mean age: 58 years; 34% had HTN, 12% T2DM, 16% CVD • Mortality: 9.6%

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Iaccarino (59)	H: 100%	Italy	1591	64	• Mean age: 67 years, 55% had HTN, 17% T2DM, 14% IHD, 12% HF • 11.8% died
Grasselli (60)	H: 100% ICU: 100%	Italy	1591	82	• Median age: 63 years, 49% had HTN, 17% T2DM, 21% CVD • 88% required invasive mechanical ventilation • 26% died
Guan (61)	H: 100% ICU: 6.2%	China	1590	57	• Mean age was 49 years; 17% had HTN, 8% T2DM, 4% CVD • 3.1% died
Alsofayan (62)	H: 71.6% ICU: 4.7%	Saudi Arabia	1519	54	• Median age: 36 years; 9% had HTN, 8% T2DM, 2% CVD • 9% were asymptomatic • Mortality: 0.65%
Rosenberg (63)	H: 100% ICU: 22.8%	USA	1438	60	• Median age: ~ 65 years, 57% had HTN, 35% T2DM, 12% IHD • 16.2% developed an arrhythmia (12.4% ventricular) and 10.2% QT prolongation • 20.3% died (of whom 18% had a cardiac arrest)
Cantador (64)	H: 100%	Spain	1419	79	• 0.2% developed an ACS, 0.5% a stroke, 0.2% a limb thrombotic event • 28.6% of those with a thrombotic event died
Cariou (65)	H: 100% ICU: 31%	France	1317	65	• Participants with T2DM; mean age: 70 years; 77% had HTN, 27% IHD, 11.6% HF • Mortality: 10.6%
Imam (66)	H: 100% ICU: 26%	USA	1305	54	• Mean age: 61 years; 56% had HTN, 30% T2DM, 16% IHD, 6% HF • 5.8% developed AKI • 15.3% died. Risk increased with age > 60 years
Fauvel (67)	H: 100% ICU: 15%	France	1240	58	• Mean age: 64 years, 45% had HTN, 22% T2DM, 11% IHD, 9.5% HF, 13.5% cancer • 91% had SR, 27% elevated Trop; 0.5% developed ACS, 8.3% a PE • 12.2% died
Bean (68)	H: 100% ICU: 30%	UK	1200	57	• Median age: 68 years, 54% had HTN, 35% T2DM, 13% IHD, 9% HF, 20% CVA • Mortality: 24%
Li (69)	H: 100%	China	1178	46	• Mean age: 55 years, 31% had HTN, 17% T2DM, 9% IHD, 2% HF • Mortality: 11%

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Chougar (70)	H: 100%	France	1176	66	• 17 participants (1.4%) developed an ischaemic stroke
Galloway (71)	H: 100% ICU: 13.5%	UK	1157	58	• Median age: 71 years; 53% had HTN, 35% T2DM, 13% IHD • Mortality: 21.1%
De Abajo (72)	H: 100% ICU: 9.7%	Spain	1139	61	• Mean age: 69 years; 54% had HTN, 27% T2DM, 27% CVD, 7% HF, 12% AF • Mortality: 24.8%
Zhang (73)	H: 100%	China	1128	54	• All with HTN; median age: 64 years, 21% had T2DM, 12% IHD, 4% CVA • 8.8% died
Luo (74)	H: 100%	China	1115	50	• Mean age: 60 years; 28% had HTN, 9% T2DM, 11% CVD • Mortality: 11.5%
Million (75)	H: 14%	France	1061	46	• Mean age: 44 years; 14% had HTN, 7% T2DM, and 4%IHD • 0.80% developed prolonged QT • Mortality: 0.75% (no ventricular arrhythmias/SCD)
Wang (76)	H: 100%	China	1012	52	• 1.4% asymptomatic; median age: 50 years; 4.5% had HTN, 2.7%T2DM, 1.5% CVD • No deaths reported
Zhao (77)	H: 100% ICU: 6%	China	1000	47	• Median age: 61 years; 28% had HTN, 12% T2DM, 6% IH. • 8.1% developed septic shock, 11.6% cardiac injury • Mortality: 11.9%
Argenziano (78)	H: 61% ICU: 23%	USA	1000	60	• Median age: 63 years; 60% had HTN, 37% T2DM, 13% IHD, 10% HF, 48% obesity • 0.9% developed a MI, 9.3% an arrhythmia, 13.8% needed renal dialysis • 21.1% died
Pan (79)	H: 100% ICU: 6.3%	China	996	47	• Mean age: ~ 59 years; 28% had HTN, 12% T2DM, 6% IHD • 20.9% developed cardiac injury • Mortality: 11.9%
López-Otero (80)	H: 24.2% ICU: 3.4%	Spain	985	44	• Mean age: 60 years; 31% had HTN, 13% T2DM, 4.4% IHD, 1.6% HFrEF, 3.8% AF • Troponin levels more likely to be elevated in those prescribed ACE-I/ARB (25.9% vs 14.5%; P = 0.028) • 3.6% developed HF • Mortality: 3.9%

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Xiong (81)	H: 100%	China	917	55	• Mean age: 49 years; 3% developed a stroke, 0.3% DVT, 0.3% arrhythmia; • 3.2% died
Chen (82)	H: 100%	China	904	47	• Median age: 56 years; 30% had HTN, 15% T2DM, 10% CVD • 10.2% died
Hu (83)	H: 100% ICU: 4.6%	China	884	51	• Mean age: ~ 45 years; 17% had HTN, 7% T2DM, 1.7% IHD. • 1.4% required ECMO • 0.11% died
Ye (84)	H: 100% ICU: 3.7%	China	856	51	• Median age: 46 years; 16.6% had HTN, 7.5% T2DM • 0.5% developed shock, 0.2% required RRT and 1.1% ECMO • Mortality: 0.1%
Rothstein (85)	H: 100%	USA	844	48	• Mean age: 59 years, 68% black • 3.3% developed a stroke (2.4 ischaemic, 0.9% intracranial haemorrhage). Of these, 39% died
Albitar (86)	NR	Worldwide	828	59	• Mean age: 49 years; 11% had HTN, 7.5% T2DM, 2% HF • Mortality: 26.4%; older age, male sex, HTN and T2DM increased risk
Lian (87)	H: 100% ICU: 2.7%	China	788	52	• Mean age: ~ 53 years, 16% had HTN, 7% T2DM • No deaths reported
Hajifathalian (88)	H: 100% ICU: 25%	USA	770	61	• Mean age: 64 years; 56% had HTN, 31%, T2DM, 21% CVD • Mortality: 11.4%
Shao (89)	H: 100%	China	761	66	• 17.8% had a cardiac arrest. The most common initial rhythm was asystole (89.7%) • 30 days survival was poor (2.9%)
Uribarri (90)	H: 100%	Worldwide	758	59	• Mean age: 66 years, 49% had HTN, 22% T2DM and 26 CVD, 8.5% CKD • 0.5% developed peripheral ischaemic event, 20% AKI • 31% died
McCullough (91)	H: 100%	USA	756	63	• Mean age: 63 years; 57% had HTN, 29% T2DM, 14% CVD, 7% HF, 37% obesity • 10.5% had T wave inversion, 7.8% RBBB, 5.6% AF, 0.7% ST-elevation (0.7%), 0.1% III degree AV block • Mortality: 11.9%
Tian (92)	H: 100%	China	751	50	• Sex- and age-matched cohort of participants with and without cancer (1:2)

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• Median age: 64 years; 39% had HTN, 26% T2DM, 10% IHD • NT-proBNP (171 (59 - 558) pg/mL) often abnormal • 14% died
Lorente-Ros (93)	H: 100% ICU: 7.6%	Spain	707	63	• Mean age: 67 years; 50% had HTN, 20% T2DM, 10% IHD, 14% HF • 21% had elevated Trop-I (> 14 ng/L) • 19.8% died, myocardial injury predicted death
Bhatla (94)	H: 100% ICU: 11%	USA	700	45	• Mean age: 50 years; 50% had HTN, 26% T2DM, 11% IHD; > 50% obesity • BNP (mean 2940 pg/mL) and troponin levels (22%) often elevated • 3.5% developed AF; 1.2% had a cardiac arrest (0.3% asystole, 0.1% TdP, 0.8% PEA) • 4% died
Nie (95)	H: 98% ICU: 2%	China	671	56	• Median age: 44 years; 9% had HTN, 2% had T2DM, 10% CVD • Mortality: 0.3%
Shi (96)	H: 100%	China	671	48	• Median age: 63 years; 30% had HTN, 15% T2DM, 9% IHD, 3% HF. • NT-proBNP (189 (67 - 494) pg/mL) often elevated; 15.8% developed cardiac injury • Mortality: 9.3%
Zhang (97)	H: 100% ICU: < 1%	China	645	51	• Mean age: ~ 45 years; 16% had HTN, 7% had T2DM. • 0.3% developed shock, 0.3% AKI • Mortality: 0%
Şenkal (98)	H: 100% ICU: 7%	Turkey	611	59	• Median age: 57 years; 41% had HTN, 23% T2DM, 11% IHD • When measured, NT-proBNP was elevated (median ~ 200 pg/mL) • 8.7% died
Barman (99)	H: 100% ICU: 32%	Turkey	607	55	• Mean age: ~ 61 years; 44% had HTN, 15% T2DM, 19% IHD • 25% had elevated troponin levels • 5% developed AKI • 17% died. Cardiac injury was associated with death
Wang (100)	H: 100%	China	605	53	• Median age: 59 years; 25.6% had HTN, 9% CVD • 0.5% developed a stroke, 13.2% cardiac injury • 18.8% died

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Gian-francesco (101)	H: 46%	Worldwide	600	29	• Participants with rheumatic disease and COVID-19 (38% RA) • Median age: 56 years; 33% had HTN, 12% T2DM, 11% CVD • 9% died
Shang (102)	H: 100% ICU: 6.5%	China	584	47	• Median age: 59 years; 34% had HTN, 14.4%T2DM and 10.6% CVD • 25% had elevated Trop-I (0.008 (0.006 - 0.014) ng/mL) • 10% developed AKI • 9.8% died
Li (103)	H: 100%	China	548	51	• Median age: 60 years; 30% had HTN, 15% T2DM, 6.2% IHD • NT-proBNP (27% > 500 ng/L) and D-dimer (45.3% > 1 g/L) were often elevated • 21% developed cardiac injury, 17% AKI • 16.5% died.
Zhang (104)	H: 100% ICU: 13.8%	China	541	47	• Mean age: 58 years; 23% had HTN, 8% had IHD, 27% CVD • 9.8% died. Patients with CVD had higher mortality (22.2%)
San Román (105)	H: 100%	Spain	522	56	• Mean age: 68 years; 50% had HTN, 18% T2DM, 8% IHD • 4% had prolonged QT • Mortality was 24.9%
Bhandari (106)	H: 100%	India	522	61	• Mean age: 36 years; 42% had HTN, 40% had T2DM, 13% IHD • 2.9% died
Lian (107)	H: 100% ICU: 1%	China	465	52	• Median age: 45 years; 17% had HTN, 6% had T2DM • 0.22% developed shock • No deaths
Suleyman (108)	H: 76.7% ICU: 39.7%	USA	463	44	• Predominance of African Americans (72%) • Mean age: 58 years; 64% had HTN, 38% T2DM, 13% IHD, 11% HF, 57% obesity • 23% had elevated hsTrop-I, 34% developed AKI • 15.5% died
Yang (109)	H: 100% ICU: 9.7%	China	462	45	• Mean age: 58 years; 27% had HTN, 16% T2DM, 8% CVD • ~ 50% had an NT-proBNP > 125 ng/L • 5.2% died
Jain (110)	H: 100% ICU: 41%	USA	459	57	• Mean age: ~ 66 years; 20% had QT prolongation, 0.2% developed an MI, and 0.2% a ventricular arrhythmia

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Brill (111)	H: 100%	UK	450	60	• Median age: 72 years; 43% had HTN, 30% T2DM and 31% CVD, 41% obesity • > 50% had an elevated D-dimer (> 1000 ng/mL), 19% developed AKI • 38% died
Xiao (112)	H: 100%	China	442	50	• 75% younger than 60 years; 14% had HTN, 7%T2DM • 2.7% died
Aloisio (113)	H: 100% ICU: 11%	Italy	427	69	• Median age: 61 years; 33% had HTN, 14% T2DM, 21% CVD • D-dimer (> 60% > 1000 ug/L) was often elevated • Mortality: 20.8%
Shi (114)	H: 100%	China	416	49	• Median age: 64 years, 31% had HTN, 14% T2DM, 11% IHD, 4% HF • Median NT-proBNP elevated (219 (73 -699) ng/L), 19.7% had cardiac injury, 1.9% AKI • Mortality: 13.7%
Gayam (115)	H: 100% ICU: 29%	USA	408	57	• African-American participants • Median age: 67 years; 66% had HTN, 43% T2DM, 13% IHD, 11% HF • BNP (58 (17 - 184) pg/mL) and D-dimer (2069 (1193 - 4491) ng/mL) often abnormal • Mortality 33%
Al-Samkari (116)	H: 100% ICU: 36%	USA	400	57	• Mean age: ~ 62 years; 31% had T2DM, 31% CVD, 41% obesity • 28.8% had HsTrop > 20 ng/L, 47% a D-dimer > 1000 ng/mL • 2.5% developed an MI, 4.8% VTE (PE: 2.5%) • Mortality: 7.2%
Patell (117)	H: 100% ICU: 51%	USA	398	53	• Mean age: 63 years; 55% had HTN, 35% T2DM, 26% CVD • 0.7% developed a stroke, 7.2% VTE (PE: 1.7%) • 20.6% died
Sinkeler (118)	H: 100%	Netherlands	397	66	• Median age: 68 years, 10% had IHD, 8% HF, 42% CKD • 0.3% developed a ventricular arrhythmia, 16% a prolonged QT
Goyal (119)	H: 100%	USA	393	61	• Median age: 62 years; 50% had HTN, 25% T2DM, 14% IHD, 7% HF, 36% obesity • 4.5% had troponin > 0.5 ng/mL, 36% D-dimer > 0.5 mg/L • 3.6% developed a MI, 3.3% VTE, 7.4% arrhythmia (0.3% ventricular), 1.8% HF

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• 10.2% died
Lodigiani (120)	H: 100% ICU: 16%	Italy	388	68	• Median age: 66 years; 47% had HTN, 23% T2DM, 14% IHD, 16% CKD • 1.1% developed a MI, 2.5% an ischaemic stroke, 2.6% a PE and 1.7% a DVT • Mortality: 26%
Liao (121)	H: 100% ICU: 23%	China	380	54	• Median age: 64 years; 30% had HTN, 16% T2DM, 6% IHD • 0.5% developed a MI, 0.3% a stroke, 0.8% VTE • 14.5% died
Myers (122)	H: 100% ICU: 30%	USA	377	56	• Median age: 61 years; 44% had HTN, 31% T2DM, 6% HF • 15.6% died
Hashemi (123)	H: 100% ICU: 36%	USA	363	55	• Mean age: 63 years; 58% had HTN, 32% T2DM, 14% IHD, 11% HF • Mortality: ~ 15%
Huang (124)	H: 100%	China	344	55	• Median age: 53 years; 23% had HTN, 11% T2DM, 5% IHD • 4.4% died
Wang (125)	H: 100%	Germany	339	49	• Median age: 69 years; 41% had HTN, 16% T2DM, 16% CVD • 10.4% developed an arrhythmia, 8.1% AKI, 21% cardiac injury and 17.4 HF • 19.2% died
Toussie (126)	H: 43%	USA	338	62	• Median age: 39 years; 16% had HTN, 12% T2DM, 40% obesity • 2.9% died
Ferrante (127)	H: 100% ICU: 22%	Italy	332	71	• Median age: 67 years; 55% had HTN, 21%T2DM, 15% IHD, 11% CVA • 39% had BNP > 100 ng/L, 37% Trop-I > 20 ng/L • 20.5% died; myocardial injury predicted death
Hu (128)	H: 100%	China	323	51	• Median age: 61 years; 32% had HTN, 14.6% T2DM, 13% CVD • 21% had HsTrop-I > 0.04 pg/mL, 30% developed an arrhythmia • 10.8% died; T2DM, old age and elevated HsTrop-I predicted poor outcomes
Biagi (129)	H: 100%	Italy	320	72	• Deceased participants with COVID-19 (30% of the original cohort) • Median age: 78 years; 73% had HTN, 23% T2DM, 12% CVD, 16% AF

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Violi (130)	H: 100%	Italy	319	60	• Mean age: ~ 60 years; 55% had HTN, 19% T2DM, 16% CVD, 20% HF • 20% died
Li (131)	H: 100%	China	312	60	• Mean age: 69 years; 57% had HTN, 39% T2DM, 30% CVD • 33% developed cardiac injury, 31% a co-agulation disorder • 6.7% died
Nie (132)	H: 100%	China	311	61	• Median age: 63 years; 33% developed cardiac injury • 35.6% died
Huang (133)	H: 100% ICU: 16.5%	China	310	56	• Median age: 62 years; 36% had HTN, 15% T2DM and 6.1% CVD; 6.8% had a CVA • BNP often elevated (67.1 (28.0 - 165.2) pg/mL) • 11% required invasive mechanical ventilation, 1.6% ECMO • 18.7% died
Shi (134)	H: 100% ICU: 12.8%	China	306	49	• Sex- and age-matched cohort of participants with and without T2DM (1:1) • Median age: 65 years; 43% had HTN, 16% CVD • 23.9% developed cardiac injury • 15.4% died
Ayanian (135)	H: 100% ICU: 23%	USA	299	54	• 68% had HTN, 46% T2DM, 46% CVD, 29% CKD • 23.7% died
Wang (136)	H: 100%	China	296	47	• Mean age: 47 years; 14% had HTN, 10% T2DM, 3% IHD • 6.4% died
Wu (137)	H: 100% ICU: 30%	China	280	54	• Mean age: 43 years; 20% had CVD • D-dimer levels not substantially elevated (0.3 (0.2 - 0.8) ug/L) • 30% needed invasive mechanical ventilation, 4.3% ECMO • No deaths reported
Chen (138)	H: 100%	China	274	62	• Median age: 62 years; 34% had HTN, 17% T2DM, 8% CVD • NT-proBNP (267 (48 - 821) pg/mL) often elevated, 44% developed cardiac injury, and 24% HF • 41% died
Han (139)	H: 100%	China	273	36	• Mean age: 58 years. 11% had NT-proBNP > 900 ng/L, 9.9% developed cardiac injury (ultra-Trop-I > 0.04 ng/mL) • 8.79% died

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Deng (140)	H: 100%	China	264	49	• Median age: 65 years; 38% had HTN, 16% T2DM, 12% IHD • Elevated NT-proBNP (227.7 (79.3 - 647.9) pg/mL) and Trop-I ultra (0.006 (0.005 - 0.016) ng/mL) • 19.7% died. Elevated Trop-I ultra and NT-proBNP predicted outcome
Okoh (141)	H: 100% ICU: 33%	USA	251	51	• Black African American and Latino Hispanic cohort • Mean age: 62 years; 70% had HTN, 46% T2DM, 20% IHD, 20% HF and 11% CVA • 24% developed septic shock, 21% AKI • 38.6% died
Yao (142)	H: 100%	China	248	54	• Mean age: ~ 62 years; 32% had HTN, 18% T2DM, 5% IHD • 74.6% had D-Dimer ≥ 0.5 mg/L • Mortality: 6.85%
Xu (143)	H: 100% ICU: 100%	China	239	60	• Critically-ill participants (13.7% of the original cohort) • Mean age: 63 years; 44% had HTN, 18% T2DM, 15% IHD • 50% developed AKI, 43% cardiac injury • 61.5% died
Cecconi (144)	H: 100% ICU: 17%	Italy	239	71	• Median age: 65 years; 50% had HTN, 22% T2DM, and 17% IHD • 27.7% had Trop-I > 19.8 ng/L • Mortality: 15.1%
Alkundi (145)	H: 100%	UK	232	63	• Mean age: 71 years; 14% had HTN, 38% T2DM, 8% CVD • 38.4% died
Masetti (146)	H: 100% ICU: 2.6%	Italy	229	65	• Median age: 61 years; 38% had HTN, 19% T2DM, 9% IHD, 8% AF • 14.4% died
Yang (147)	H: 100%	China	226	50	• Mean age: ~ 55 years; 37% had HTN, 20% T2DM, 6% IHD • 22% died
Yu (148)	H: 100% ICU: 100%	China	226	61	• Median age: 64 years; 43% had HTN, 21% had T2DM, 10% IHD • D-dimer was > 1 mg/L in 80% • 9.3% developed arrhythmia (ventricular: 0.4%); 27% cardiac injury; 38.5% died
Obata (149)	H: 100% ICU: 24%	USA	225	57	• Mean age: ~ 67 years; 60% had HTN, 32% T2DM, 20% IHD, 12% HF, 6.6% CVA • 0.4% had a ventricular arrhythmia; 5.3% required CPR • 18.2% died

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Li (150)	H: 100%	China	225	53	• Mean age: 50 years; 21% had HTN, 39% T2DM, 30% CVD • 0.89% died
Deng (151)	H: 100%	China	225	55	• Mean age: ~ 55 years; 26% had HTN, 12% T2DM, 7.6% CVD • 8.9% developed AKI, 29.3% cardiac injury • 48.4% died
Pelayo (152)	H: 100%	USA	223	52	• Predominance of African American participants (68%) • Mean age: 66 years; 81% had HTN, 47% T2DM, 16% IHD, 11% HF • 19% required vasopressors, 49% developed AKI • 19.7% died
Güner (153)	H: 100% ICU: 18.9%	Turkey	222	60	• Mean age: 51 years; 23% had HTN, 14% T2DM, 7% IHD, 24% CVD • 1.3% developed a PE, 0.45% DVT, 0.9% shock • 5.4% died
Zhang (154)	H: 100% ICU: 19.9%	China	221	49	• Median age: 55 years; 24% had HTN, 10% T2DM, 10% CVD • 10.9% developed an arrhythmia, 7.7% cardiac injury • 5.4% died
Li (155)	H: 100%	China	219	41	• Of those who developed a stroke (5.1%; 4.6% ischaemic, 0.5% intracerebral haemorrhage), 54% died
Mao (156)	H: 100%	China	214	41	• Mean age: 53 years; 24% had HTN, 14%T2DM • 2.8% developed a stroke • 2.8% died
Yang (157)	H: 100%	China	212	51	• Median age: 56 years; 15.6% had IHD, 5.2% CKD • 10.30% developed cardiac injury • Mortality: 11.80%
Gao (158)	H: 100% ICU: 9%	China	210	48	• Median age: 71 years; 55% had HTN, 18% T2DM, 25% CVD • 75% had D-dimer > 0.5 ug/mL, 1% developed a stroke, 2% AKI • 16.7% died
Li (159)	H: 100%	China	204	49	• Median age: 68 years; 36% had HTN, 18% T2DM, 22% CVD • 13.8% developed AKI, 12.9% cardiac injury • 37.2% died

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Wu (160)	H: 100% ICU: 26.4%	China	201	64	• Median age: 51 years; 19% had HTN, 11% T2DM, 4% CVD • Elevated D-dimer (0.61 (0.35 - 1.28) ug/mL) • Mortality: 21.9%; increasing age and D-dimer predicted poorer outcomes
Pagnesi (161)	H: 100% ICU: 3.5%	Italy	200	66	• Median age: 62 years; 42% had HTN, 19% T2DM, 8.5% IHD, 11% AF • Elevated NT-proBNP (256 (89 - 707) pg/mL) and HsTrop-T (13.6 (6.0 - 30.0) ng/L) • 14.5% had impaired RVEF, ~ 4% impaired LVEF • 9.5% died
Yang (162)	H: 100% ICU: 14.5%	China	200	49	• Mean age: 55 years; 22% had HTN, 11% had T2DM, 6% CVD • 10% developed cardiac injury, 12% AKI • 7.5% died (> 50% in ICU)
Middeldorp (163)	H: 100% ICU: 38%	Netherlands	198	66	• Mean age: 61 years; 5.6% had a VTE, 3.5% Ca, and > 25% were obese • Elevated D-Dimer (84% > 0.5 mg/L); 20% developed VTE (PE: 6.6%) • 19% died
Yan (164)	H: 100% ICU: 47.7%	China	193	59	• Median age: 64 years; 38% had HTN, 25% T2DM, 16% CVD • Median NT-proBNP (665 ng/L vs 259 ng/L) was higher in those with T2DM than in those without • Mortality: 56%
Russo (165)	H:100%	Italy	192	60	• Mean age: 68 years; 58% had HTN, 22% T2DM, 14% IHD, 10% HF; 18.2% died.
Zhou (166)	H: 100% ICU: 26%	China	191	62	• Median age: 56 years; 30% had HTN, 19%T2DM, 8% IHD • 17% developed cardiac injury, 23% HF • Mortality 28.3%
Guo (167)	H: 100%	China	187	49	• Mean age: 59 years; 33% had HTN, 15% T2DM, 11% IHD, 3% HF • Elevated NT-proBNP (268 (75 - 689) pg/ml); 27.8% had elevated TnT levels • 5.9% developed a ventricular arrhythmia • 23% died
Klok (168)	H: 100% ICU: 100%	Nethether-lands	184	76	• Mean age: 64 years; 2.7% had a cancer • 1.6% developed a stroke, 15.2% VTE (PE: 13.6%) • 13% died
Ni (169)	H: 100%	China	176	57	• Median age: 67 years, 49% had HTN, 27%T2DM, 14% IHD

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• 27.8% developed cardiac injury • 34% died
Chen (170)	H: 100% ICU: 2%	China	175	50	• Mean age: 45 years, 16% had HTN, 7% T2DM • 20% had an abnormal ECG, 18% severe hypokalaemia (potassium < 3 mmol/L)
Guo (171)	H: 100%	China	174	44	• Median age: 59 years; 25% had HTN, 21% T2DM, 18% CVD • 5.2% died
Mahévas (172)	H: 100%	France	173	72	• Median age: 60 years; 9% had T2DM, 51% CVD, and 4% HF, 26% obesity • 0.5% developed I degree AV-block, and 4.1% a prolonged QT • 10% died
Si (173)	H: 100%	China	170	55	• Only participants with cardiac injury (out of 1159; 14.7%) • Mean age: ~ 62 years; 56% had HTN, 22% T2DM, 18% IHD • 2.3% developed a stroke, 25.9% an arrhythmia (5.3% ventricular) and ~ 9% had a prolonged QT interval • Mortality: 71.2% (vs 6.5% in those without cardiac injury)
Zhang (174)	H: 100% ICU: 4.2%	China	166	51	• Mean age: 63 years; 46% had HTN, 37% T2DM, 18% CVD • Median NT-proBNP was elevated (179 (67 - 457) pg/ml); 10.2% had Trop-I > 15.6 pg/ml; • 14.5% died
Itelman (175)	H: 100% ICU:14.8%	Israel	162	65	• Mean age: 52 years; 30% had HTN, 19%T2DM, 7% IHD, 19% obesity • 3.1% died
Shi (176)	H: 100% ICU: 100%	China	161	65	• Mean age: 59 years, 27% had HTN, 16% T2DM, 5% IHD • 1.24% developed a MI, 1.86% a ventricular arrhythmia, 5.59% HF • 31% died
Lim (177)	H: 100%	South Korea	160	54	• Mean age: ~ 69 years; 48% had HTN, 31% T2DM, 13% IHD and 6.3% HF • 18.3% developed AKI • 26.3% died (AKI: 56.7%; no AKI: 20.8%)
Andrikopoulou (178)	H: 55% ICU: 6% OP: 45%	USA	158	0	• Mean age: ~ 30 years; 5% had HTN (5%), 2% T2DM • Only 1 participant (0.6%) had troponin > 14 ng/L • 0.6% developed AKI • no deaths

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Zou (179)	H: 100% ICU: 100%	China	154	44	• Mean age: 61 years, 31% had HTN, 26% T2DM, 15% IHD • 23% developed shock, 16% AKI, 29% cardiac injury • 33.7% died
Ren (180)	H: 100%	China	151	52	• Mean age: 60 years, 40% had HTN, 26% T2DM, 11% CVD • 9.9% required mechanical ventilation • 22% died
Ruan (181)	H: 100% ICU: 29%	China	150	68	• Mean age: 57 years; 33% had HTN, 17% T2DM, 9%CVD • 18% developed HF • 45% died
Oussalah (182)	H: 100%	France	149	61	• Median age: 65 years; 50% had HTN, 29% T2DM, 29% CVD • ~ 75% NT-proBNP > 125 ng/L, ~ 50% elevated HsTrop-I • 1% developed a PE • 13% died
Chen (183)	H: 100% ICU: 0.7%	China	145	55	• Mean age: 48 years; 15% had HTN, 10% T2DM • no deaths reported
Bonetti (184)	H: 100%	Italy	144	67	• Median age: 70 years, 26% had T2DM and 49% CVD • Mortality: 48.6%
Xie (185)	H: 100%	China	140	51	• Median age: 60 years, 28% had HTN, 14% T2DM, 6% CVD • Mortality: 25.7%
Gavin (186)	H: 100%	USA	140	51	• Mean age: 60 years; 69% had HTN, 36% T2DM, 19% IHD, 16% HF, 53% obesity • BNP was > 400 pg/mL in > 25%; >75% had D-dimer > 500 ng/mL • 10.7% developed VTE, 15% arrhythmia, 29% AKI; 15% • 7% died
Wang (187)	H: 100% ICU: 26%	China	138	54	• Median age: 56 years; 31% had HTN, 10% T2DM, 14% CVD • 16.7% developed an arrhythmia, 7.2% cardiac injury • 4.3% died
Liu (188)	H: 100%	China	137	45	• Median age: 57 years; 10% had HTN, 10% T2DM, 7% CVD • 11.7% died
Yang (189)	H: 100% ICU: 24%	China	136	49	• Median age: 56 years; 27% had HTN, 15% T2DM, 7% CVD

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• 8.1% developed cardiac injury • 16.9% died
Zhang (190)	H: 100% ICU: 100%	China	136	63	• Mean age: 69 years; 50% had HTN, 40% T2DM • ~ 90% had NT-proBNP > 125 ng/L; 2% developed VTE, 54% cardiac injury, 5% required ECMO • 72% died
Koleilat (191)	H: 100%	USA	135	54	• Mean age: ~ 63 years; 70% had HTN, 38% T2DM, 12% IHD • 13.3% developed a DVT, 3.7% a PE • 14.8% died
Wan (192)	H: 100% ICU: 29.6%	China	135	53	• Median age: 47 years; 10% had HTN, 9% T2DM, 5% CVD • 0.7% developed shock, 3.7% AKI, 7.4% cardiac injury • 0.7% died
Li (193)	H: 100% ICU: 14.4%	China	132	53	• All participants with T2DM. Median age: 65 years, 64% had HTN, 14% CVD, 9% CVA • HsTrop-I > 26.2 pg/mL in 16.7%; 6.1% developed cardiac injury • 11.4% died
Sala (194)	H: 100%	Italy	132	66	• Mean age: 65 years; 45% had HTN, 20% T2DM, 7% IHD, 12% AF • 9% developed a supraventricular arrhythmia (AF: 6%), none a QTc > 450ms
Wang (195)	H: 100%	China	132	52	• Median age was 66 years; 50% had HTN, 33% T2DM, 17% CVD • 16.7% died
Xiong (196)	H: 100%	China	131	57	• Participants receiving maintenance haemodialysis • Mean age: 63 years; 26% had HTN, 27% T2DM, 69% CVD • 9.6% developed a cerebrovascular event, 28% cardiac injury • 31% died
Wu (197)	H: 100%	China	125	53	• Median age: 55 years; 28% had HTN, 20% T2DM, 9% IHD • Median BNP was 65 (23 - 178) pg/mL; 8% had Trop-I > 34.2 pg/mL
Churchill (198)	H: 100% ICU: 69%	USA	125	60	• Mean age: 64 years; 60% had HTN, 41% T2DM, and 50% were obese • 22% had LVEF < 50%; elevated NT-proBNP (1643 pg/mL (374 - 8278 pg/mL))
Pan (199)	H: 100% ICU: 73%	China	124	68	• Median age: 68 years; 50% had HTN, 20% T2DM, 15% CVD

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• BNP (79.3 (30.4 - 164.5) ng/L) and Trop-I (19.3 (8.4 - 96.4) ug/L) often abnormal • 71.8% died
Simonnet (200)	H: 100% ICU: 100%	France	124	73	• Median age: 60 years; 49% had HTN, 23% T2DM, 47% obesity • Mortality: 15%
Luan (201)	H: 100% ICU: 30%	China	117	53	• Mean age: 62 years; 20% had HTN, 10% T2DM • 6.8% developed shock, 4% AKI, 2.6% HF • 1.7% died
Yang (202)	H: 100%	China	114	49	• Mean age: 47 years; 10% had CVD • No deaths reported
Shang (203)	H: 100%	China	113	65	• Median age: 66 years; 44% had HTN, 18% T2DM, 25% had IHD • 44% had D-dimer > 0.5 ug/mL, 23% developed AKI, 38.9% cardiac injury • 43% died; old age, IHD, and increasing D-dimer predicted poor outcome
Selçuk (204)	H: 100% ICU: 39%	Turkey	113	52	• Median age: ~ 64 years, 43% had T2DM, 25% IHD, 8% HF • Mortality: 30.9%
Deng (205)	H: 100% ICU: 23%	China	112	51	• Median age: 65 years; 32% had HTN, 17% T2DM, 13% had IHD, 4% AF • Median NT-proBNP was 430 (101-2859) ng/L, 37.5% had Trop-I > 0.04 ng/ml • 7% had AV-block, 19% abnormal ST-T changes, 4% AF • 5.4% had LVEF < 50%, 1 participant had an MI • Mortality: 12.5%
Zhang (206)	H: 100% ICU: 16.2%	China	111	45	• Median age 38 years, 13% had HTN, 13% T2DM, 3% CVD • 0.9% required ECMO • Mortality: 13.5%
Quartuccio (207)	H: 100% ICU: 24%	Italy	111	69	• Mean age: 59 years; 37% had HTN • 23% required mechanical ventilation • 3.6% died
Sud (208)	H: 100% ICU: 30%	USA	110	64	• Mean age: 66 years • 22% had myocardial injury, of whom 1/5 had h/o IHD; ECG suggested STEMI (n = 3) or pericarditis (n = 1), 54% had cardiac dysfunction at echocardiography • In those without myocardial injury, 25% had LV dysfunction, with or without RV dysfunction (30%)

Table 2. Key findings of the 220 studies included in the review *(Continued)*

Zhou (209)	H: 100%	China	110	55	• Mean age: 58 years; 33% had HTN, 10% T2DM, 9% CVD • 8.2% died
Du (210)	H: 100% ICU: 46.8%	China	109	68	• Deceased participants • Mean age: 71 years; 60% had HTN, 31% T2DM, 34% CVD
Yao (211)	H: 100% ICU: 16%	China	108	40	• Median age: 52 years; 15% had HTN, 4.6% T2DM • D-Dimer was > 1 ug/ml in 37%, 6% developed shock, 7.2% cardiac injury • 11% died
Escalera-Antezana (212)	H: 13.1% ICU: 3.7%	Bolivia	107	51	• Mean age: 44 years; 9% had HTN, 5% T2DM, 2% HF • Mortality: 5.6%; risk increased with age > 60 years and HTN
Wang (213)	H: 100%	China	107	53	• Median age: 51 years; 23% had HTN, 10% T2DM, 12% CVD • 0.9% had a MI, 0.9% a ventricular arrhythmia, 11.20% cardiac injury • 17.8% died
Argulian (214)	H: 100%	USA	105	64	• Mean age: 66 years; mean LVEF 55%, 31% had RV dilatation • 20% died (41% of those with RV dilatation vs 11% of those without)
Hsia (215)	H: 100%	USA	105	58	• Mean age: 67 years, 49% had HTN, 39% T2DM, 5% IHD, 19% AF • 20% developed a prolonged QT, 10.5% an arrhythmia (1% ventricular) • 27.6% died
Zou (216)	H: 100%	China	105	53	• Participants with chronic HBV infection • Median age: 62 years; 26% had HTN, 9% T2DM, 7% IHD • 13.3% developed cardiac injury • 6.7% died
Buckner (217)	H: 100%	USA	105	50	• Median age: 69 years; 59% had HTN, 33% T2DM, 38% CVD, 19%HF, 47% obesity • 19% had cardiac injury • Mortality: 33%
Xie (218)	H: 100%	China	105	51	• Mean age: 44 years; 10% had HTN, 13% had T2DM, 9% CVD • No deaths
Marone (219)	H: 100%	Italy	105	NR	• Participants with suspected DVT; 41% had DVT, 23.8% PE (2/3 in absence of a DVT)
Guo (220)	H: 100%	China	105	46	• Median age: 67 years; 44% had HTN, 26% T2DM, 16% CVD

Table 2. Key findings of the 220 studies included in the review *(Continued)*

					• 4.8% developed cardiac injury • 2.9% died
Hu (221)	H: 100%	China	105	59	• Mean age: ~ 60 years; 27% had HTN, 3% T2DM, 6% CVD • 18.1% died
Hwang (222)	H: 100% ICU: 25%	China	103	50	• Mean age: 67 years; 55% had HTN, 34% T2DM, 12% CVD • 4% required ECMO • 25% died
Zhu (223)	H: 100%	China	102	58	• Mean age: 65 years; 28% died
Wu (224)	H: 100% ICU: 4%	China	101	54	• Mean age:~ 62 years; 67% had HTN, 39% T2DM, 15% CVD, 49% on haemodialysis • Arrhythmias (18 vs 2%) and cardiac injury (29 vs 8%) were more common in those on haemodialysis • 8.9% died (14% on haemodialysis)
Duanmu (225)	H: 24% ICU: 6%	USA	100	56	• Median age: 45 years; 19% had HTN, 10% T2DM, 22% obesity • 4% required intubation • 1% died
Moriconi (226)	H: 100%	Italy	100	52	• Mean age: 70 years; 53% had HTN, 25% T2DM, 28% HF, 29% obese • 18% died

Abbreviations used: H- hospital; OP – Outpatient; IP – inpatients; ICU – intensive care; CKD – chronic kidney disease; IHD – ischaemic heart disease; h/o - history of; HTN – hypertension; T2DM – type 2 diabetes mellitus; HF – heart failure; CVD – cardiovascular disease; NR – not reported; MI – myocardial infarction; AF – atrial fibrillation; RCT – randomised controlled trial; ECMO - Extra Corporeal Membrane Oxygenation; Trop – Troponin; HsT-I – High sensitivity troponin-I; LVEF – left ventricular ejection fraction; RVEF – right ventricular ejection fraction; Y – years; VTE – venous thromboembolism; PE: pulmonary embolism; DVT - deep vein thrombosis; TdP - torsades de pointes; PEA - pulseless electrical activity; SR- sinus rhythm; CVA - Cerebrovascular accident; AKI – acute kidney injury, SCD – sudden cardiac death.

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Cardiovascular Diseases] explode all trees

#2 (heart* or cardiac* or coronary or cardio*)

#3 myocardial infarct*

#4 ACS

#5 MeSH descriptor: [Stroke] explode all trees

#6 stroke*

#7 cerebral vascular

#8 cerebrovasc*

#9 apoplexy

#10 (brain near/2 accident*)

#11 ((brain* or cerebral or lacunar) near/2 infarct*)

#12 Peripheral arterial

#13 MeSH descriptor: [Thrombosis] explode all trees

#14 thrombosis*

#15 pulmonary thromboembolism

#16 Arrhythmia*

#17 Supraventricular tachycardia

#18 (SVT or PSVT)

#19 atrial fibrillat*

#20 atrial flutter*

#21 (atrioventricular near/2 block)

#22 av block

#23 ventricular tachycardia*

#24 MeSH descriptor: [Shock] this term only

#25 (circulatory near/1 (failure or collapse))

#26 peripheral vascular failure

#27 MeSH descriptor: [Ultrafiltration] this term only

#28 Ultrafiltration

#29 MeSH descriptor: [Dialysis] this term only

#30 Dialysis

#31 Myocarditis

#32 MeSH descriptor: [Troponin] this term only

#33 Troponin*

#34 MeSH descriptor: [Natriuretic Peptide, Brain] this term only

#35 (BNP or NTproBNP)

#36 brain natriuretic peptide

#37 b-type natriuretic peptide

#38 type-b natriuretic peptide

#39 Ferritin

#40 Left ventricular ejection fraction

#41 LVEF

#42 MeSH descriptor: [Ventricular Dysfunction, Right] explode all trees

#43 MeSH descriptor: [Ventricular Dysfunction, Left] explode all trees

#44 (ventricular near/2 (function or dysfunction))

#45 ((rv or lv) near/2 (function or dysfunction))

#46 TAPSE

#47 Tricuspid annular plane systolic excursion

#48 prolonged QT interval

#49 QTc prolong*

#50 {OR #1-#49}

#51 ((coronavirus* or corona virus*) and (Huanan or Hubei or Wuhan))

#52 coronavirus 19

#53 coronavirus disease 2019

#54 (COVID 19 or Covid 2019 or COVID19)

#55 (2019 nCoV or nCoV 2019 or "2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV")

#56 ((new or novel or nouveau) near/1 (corona virus* or coronavirus*))

#57 ("SARS-CoV2" or "SARS CoV-2" or SARSCoV2 or "SARSCoV-2")

#58 (SARS-coronavirus-2 or Sars-coronavirus2 or SARS-like coronavirus)

#59 (Severe Acute Respiratory Syndrome Coronavirus-2 or severe acute respiratory syndrome coronavirus 2)

#60 {OR #51-#59}

#61 #50 AND #60

MEDLINE Ovid

1 exp Cardiovascular Diseases/ (2381633)

2 (heart* or cardiac* or coronary or cardio*).tw. (1810527)

3 myocardial infarct*.tw. (193775)

4 ACS.tw. (21863)

5 exp Stroke/ (134474)

6 stroke*.tw. (246937)

7 cerebral vascular.tw. (5878)

8 cerebrovasc*.tw. (53962)

9 apoplexy.tw. (3061)

10 (brain adj2 accident*).tw. (170)

11 ((brain* or cerebral or lacunar) adj2 infarct*).tw. (26487)

12 Peripheral arterial.tw. (15393)

13 exp Thrombosis/ (129307)

14 thrombosis*.tw. (131401)

15 pulmonary thromboembolism.tw. (3492)

16 Arrhythmia*.tw. (84689)

17 Supraventricular tachycardia.tw. (5984)

18 (SVT or PSVT).tw. (2405)

19 atrial fibrillat*.tw. (69770)

20 atrial flutter*.tw. (5673)

21 (atrioventricular adj2 block).tw. (8105)

22 av block.tw. (3777)

23 ventricular tachycardia*.tw. (23563)

24 Shock/ (17596)

25 (circulatory adj1 (failure or collapse)).tw. (3276)

26 peripheral vascular failure.tw. (17)

27 Ultrafiltration/ (10114)

28 Ultrafiltration.tw. (15384)

29 Dialysis/ (12612)

30 Dialysis.tw. (106983)

31 Myocarditis.tw. (15115)

32 Troponin/ (5434)

33 Troponin*.tw. (25983)

34 Natriuretic Peptide, Brain/ (14223)

35 (BNP or NTproBNP).tw. (10586)

36 brain natriuretic peptide.tw. (9017)

37 b-type natriuretic peptide.tw. (7278)

38 type-b natriuretic peptide.tw. (70)

39 Ferritin.tw. (27639)

40 Left ventricular ejection fraction.tw. (25691)

41 LVEF.tw. (13360)

42 exp Ventricular Dysfunction, Right/ (5857)

43 exp Ventricular Dysfunction, Left/ (30656)

44 (ventricular adj2 (function or dysfunction)).tw. (57724)

45 ((rv or lv) adj2 (function or dysfunction)).tw. (18116)

46 TAPSE.tw. (916)

47 Tricuspid annular plane systolic excursion.tw. (1126)

48 prolonged QT interval.tw. (1029)

49 QTc prolong*.tw. (1747)

50 or/1-49 (3513853)

51 ((coronavirus* or corona virus*) and (Huanan or Hubei or Wuhan)).tw. (1876)

52 "coronavirus 19".tw. (63)

53 "coronavirus disease 2019".tw. (5722)

54 (COVID 19 or Covid 2019 or COVID19).tw. (30069)

55 (2019 nCoV or nCoV 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV).tw. (757)

56 ((new or novel or nouveau) adj1 (corona virus* or coronavirus*)).tw. (3985)

57 ("SARS-CoV2" or "SARS CoV-2" or SARSCoV2 or "SARSCoV-2").tw. (8835)

58 (SARS-coronavirus-2 or Sars-coronavirus2 or SARS-like coronavirus).tw. (125)

59 (Severe Acute Respiratory Syndrome Coronavirus-2 or severe acute respiratory syndrome coronavirus 2).tw. (2810)

60 or/51-59 (34488)

61 50 and 60 (3306)

62 exp animals/ not humans.sh. (4720043)

63 61 not 62 (3302)

64 limit 63 to yr="2019-current" (3294)

Embase Ovid

1 exp cardiovascular disease/ (3889105)

2 (heart* or cardiac* or coronary or cardio*).tw. (2404039)

3 myocardial infarct*.tw. (263323)

4 ACS.tw. (41000)

5 exp cerebrovascular accident/ (208843)

6 stroke*.tw. (388455)

7 cerebral vascular.tw. (7222)

8 cerebrovasc*.tw. (75586)

9 apoplexy.tw. (2732)

10 (brain adj2 accident*).tw. (225)

11 ((brain* or cerebral or lacunar) adj2 infarct*).tw. (37380)

12 Peripheral arterial.tw. (21738)

13 exp thrombosis/ (309475)

14 thrombosis*.tw. (188875)

15 pulmonary thromboembolism.tw. (4804)

16 Arrhythmia*.tw. (119667)

17 Supraventricular tachycardia.tw. (7816)

18 (SVT or PSVT).tw. (4623)

19 atrial fibrillat*.tw. (124088)

20 atrial flutter*.tw. (8681)

21 (atrioventricular adj2 block).tw. (10044)

22 av block.tw. (6637)

23 ventricular tachycardia*.tw. (33353)

24 cardiogenic shock/ or shock/ (51606)

25 (circulatory adj1 (failure or collapse)).tw. (3922)

26 peripheral vascular failure.tw. (13)

27 ultrafiltration/ (21224)

28 Ultrafiltration.tw. (20167)

29 dialysis/ (48631)

30 Dialysis.tw. (141767)

31 Myocarditis.tw. (19668)

32 troponin/ (20922)

33 Troponin*.tw. (44425)

34 brain natriuretic peptide/ (29484)

35 (BNP or NTproBNP).tw. (26084)

36 brain natriuretic peptide.tw. (14139)

37 b-type natriuretic peptide.tw. (11030)

38 type-b natriuretic peptide.tw. (115)

39 Ferritin.tw. (39650)

40 Left ventricular ejection fraction.tw. (45951)

41 LVEF.tw. (40812)

42 exp heart right ventricle function/ (8194)

43 exp heart left ventricle function/ (44038)

44 (ventricular adj2 (function or dysfunction)).tw. (88055)

45 ((rv or lv) adj2 (function or dysfunction)).tw. (41173)

46 TAPSE.tw. (4272)

47 Tricuspid annular plane systolic excursion.tw. (2891)

48 prolonged QT interval.tw. (1561)

49 QTc prolong*.tw. (3172)

50 or/1-49 (4942750)

51 ((coronavirus* or corona virus*) and (Huanan or Hubei or Wuhan)).tw. (1723)

52 "coronavirus 19".tw. (60)

53 "coronavirus disease 2019".tw. (4864)

54 (COVID 19 or Covid 2019 or COVID19).tw. (26529)

55 (2019 nCoV or nCoV 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV).tw. (677)

56 ((new or novel or nouveau) adj1 (corona virus* or coronavirus*)).tw. (3611)

57 ("SARS-CoV2" or "SARS CoV-2" or SARSCoV2 or "SARSCoV-2").tw. (7482)

58 (SARS-coronavirus-2 or Sars-coronavirus2 or SARS-like coronavirus).tw. (118)

59 (Severe Acute Respiratory Syndrome Coronavirus-2 or severe acute respiratory syndrome coronavirus 2).tw. (2339)

60 or/51-59 (30597)

61 50 and 60 (4272)

62 (animal/ or nonhuman/) not human/ (5599194)

63 61 not 62 (4252)

64 limit 63 to yr="2019-current" (4230)

65 limit 64 to embase (3018)

Cochrane COVID-19 Study Register

(heart* OR cardiac* OR coronary OR cardio*)

ClinicalTrials.Gov

COVID-19 AND (heart* OR cardiac* OR coronary OR cardio*)

EU Clinical Trials Register

covid-19 AND (heart* OR cardiac* OR coronary OR cardio*)

Appendix 2. Search overview

Database searched	Date searched	Number of results
CENTRAL Issue 7 of 12, 2020 (Cochrane Library)	24 July 2020	151
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 22 July 2020)	24 July 2020	3294
Embase (Ovid, 1980 to 2020 week 29)	24 July 2020	3018
Cochrane COVID-19 Study Register	24 July 2020	1486
ClinicalTrials.gov	24 July 2020	75
EU Clinical Trials Register	24 July 2020	60
Total		**8,084**
After de-duplication		**5464**

Appendix 3. References

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WHAT'S NEW

Date	Event	Description
7 April 2022	Amended	Reviews content amended according to an external feedback that did not change the objectives, scope or criteria for including studies. Conclusions not changed. See Acknowledgements.

HISTORY

Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

PP and JGFC drafted the protocol, which was critically revised and approved by all authors, and coordinated the review.
Five authors (KSL, PP, GD, CW, KM) reviewed titles and abstracts to determine their eligibility, and extracted data.
KSL, GD, CW, and KM assessed the quality of the studies.
PP and JGFC drafted the manuscript.
All authors critically revised and approved the final version of the manuscript.

DECLARATIONS OF INTEREST

PP declares no conflicts of interest.

GD declares no conflicts of interest.

CMW declares no conflicts of interest.

KSL declares no conflicts of interest.

KM declares grants to the institution from Chief Scientist Office, EPSRC Impact Acceleration Account (IAA) and Wellcome ISSF COVID Response Fund for research on COVID-19. KM is involved in clinical duties involving patients with COVID-19 and potential cardiovascular complications at NHS Greater Glasgow and Clyde, UK.

MA declares no conflicts of interest.

CB declares grants to the institution from the Chief Scientist Office for research on COVID-19. CB treats patients with COVID-19 at the Queen Elizabeth University Hospital, Glasgow, UK. CB also declares involvement in eligible studies for this review.

IS declares no conflicts of interest.

PDL declares no conflicts of interest.

AL has received speaker, advisory board or consultancy fees from Pfizer, Novartis, Servier, Astra Zeneca, Bristol Myers Squibb, Amgen, Takeda, Roche, Janssens-Cilag Ltd, Clinigen Group, Eli Lily, Eisai Ltd, Ferring Pharmaceuticals, Boehringer Ingelheim, Akcea Therapeutics, Myocardial Solutions, iOWNA Health and Heartfelt Technologies Ltd. AL works as a Honorary Consultant Cardiologist for the Royal Brompton and Harefield Hospital NHS Trust.

AMcC declares no conflicts of interest.

RST declares no conflicts of interest.

JGFC declares funds to the institution from Vifor, Pharmacosmos, Ergofigure, Viscardia, Innolife, Pharmanord, Bayer; funds fore lecturers received by JGFC from Amgen, AstraZeneca, Bayer, Novartis, Servier, Vifor. JGFC also contributes to advisory boards of Amgen, Bayer, Novartis, Servier, Vifor and has received funds via the instititution for participating on a Data and Safety Monitoring Board for Idorsia.

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- No sources of support provided

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to the large number of papers, two review authors, from a pool of five (KSL, PP, GD, CW, KM) independently reviewed titles and abstracts to determine their eligibility. A second review author checked 100% (and not 20%, as stated in the protocol) of excluded records.

A second review author checked 100% (and not 20%, as stated in the protocol) of extracted data.

Four review authors (KSL, GD, CW, and KM) independently assessed the quality of the studies using the Joanna Briggs Institute (JBI) checklist for prevalence studies and the JBI checklist for case series, respectively.

Due to the large amount of articles identified and the substantial amount of time required to conduct this review, we decided not to screen for additional publications in references and did not contact authors to request additional details if they were not reported in the main publication.

During peer-review, editors suggested removing raised ferritin from the outcomes of interest, as they felt that elevated ferritin was not a cardiovascular complication of COVID-19.

We excluded manuscripts enrolling only paediatric (< 18 years) participants.

INDEX TERMS

Medical Subject Headings (MeSH)

Arrhythmias, Cardiac [epidemiology]; Cardiovascular Diseases [*epidemiology]; Comorbidity; COVID-19 [*epidemiology] [mortality]; Diabetes Mellitus [epidemiology]; Heart Failure [epidemiology]; Hospitalization [statistics & numerical data]; Hypertension [epidemiology]; Incidence; Myocardial Ischemia [epidemiology]; Obesity [epidemiology]; Prevalence; Thrombosis [epidemiology]

MeSH check words

Humans