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COVID-19 postacute care major organ damage: a systematic review

Nancy Greer ,[1] Bradley Bart,[2,3] Charles J Billington,[2,4] Susan J Diem,[1,2,5,6] Kristine E Ensrud,[1,2,5,6] Anjum Kaka,[2,7] Mark Klein,[2,8] Anne C Melzer,[2,9] Scott Reule,[2,10] Aasma Shaukat,[1,2,11] Kerry Sheets,[1,2,12] Jamie Starks,[2,13] Orly Vardeny,[1,2,14] Lauren McKenzie,[1] Benjamin Stroebel,[1] Roderick Macdonald,[1] Katie Sowerby,[1] Wei Duan-Porter,[1,2,5] Timothy J Wilt[1,2,5,15]

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For numbered affiliations see end of article.

Correspondence to
Dr Nancy Greer;
nancy.greer@va.gov

ABSTRACT

Background Major organ complications have been reported in patients hospitalised for COVID-19; most studies lacked controls.

Objective Examine major organ damage postdischarge among adults hospitalised for COVID-19 versus non-COVID-19 controls.

Data sources MEDLINE, Embase and Cochrane Library from 1 January 2020 to 19 May 2021.

Study eligibility criteria English language studies of adults discharged from hospital for COVID-19; reporting major organ damage. Single review of abstracts; independent dual review of full text.

Study appraisal and synthesis methods Study quality was assessed using the Joanna Briggs Institute Appraisal Checklist for Cohort Studies. Outcome data were not pooled due to heterogeneity in populations, study designs and outcome assessment methods; findings are narratively synthesised.

Results Of 124 studies in a full evidence report, 9 included non-COVID controls and are described here. Four of the nine (three USA, one UK) used large administrative databases. Four of the remaining five studies enrolled <600 COVID-19 patients. Mean or median age ranged from 49 to 70 years with 46%–94% male and 48%–78% White race; 10%–40% had been in intensive care units. Follow-up ranged from 4 weeks to 22 weeks postdischarge. Four used hospitalised controls, three non-hospitalised controls and two were unclear. Studies used various definitions of, and methods to assess, major organ damage outcomes. While the magnitude of effect differed across studies, incident cardiac, pulmonary, liver, acute and chronic kidney, stroke, diabetes, and coagulation disorders were consistently greater in adults hospitalised for COVID-19 compared with non-COVID-19 controls.

Limitations Applicability to subgroups (age, gender, COVID-19 severity, treatment, vaccination status) and non-hospitalised patients is unknown.

Conclusions and implications of key findings Postacute COVID-19 major organ damage is common and likely higher than controls. However, there is substantial uncertainty. More consistent reporting of clinical outcomes and pre-COVID health status along with careful selection of control groups are needed to address evidence gaps.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review examines clinically relevant major organ damage following hospitalisation for COVID-19 as reported in studies with a non-COVID-19 comparator group.
⇒ We defined 'postacute COVID-19' as posthospital discharge; applicability of findings to non-hospitalised patients with acute COVID-19 symptoms is unclear.
⇒ Meta-analysis was inappropriate due to heterogeneity in populations, study designs and methods of outcome assessment.

INTRODUCTION

COVID-19 is a viral illness that, as of 2 May 2022, was identified in over 511 million individuals (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Over 6.2 million deaths worldwide are attributed to COVID-19. In addition to the potential for severe acute pulmonary disease associated with coronavirus infections, there have been numerous reports of other major organ system manifestations and complications in patients hospitalised for COVID-19.[1–12] These studies typically lacked controls without COVID-19 and it is not clear if postdischarge major organ system damage differs in patients hospitalised for COVID-19 from similar individuals without COVID-19.

Multiorgan damage[13] and long-term clinical outcomes[14] following infection with other coronaviruses, such as SARS and Middle East respiratory syndrome, have been previously reported. Because many COVID-19 patients are admitted to intensive care units (ICUs), outcomes similar to those observed in postintensive care syndrome or postsepsis syndrome may be long-term consequences of COVID-19.[15]

We assessed postacute care major organ damage prevalences in adults hospitalised for COVID-19 and determined if these differ compared with adults without COVID-19. Our review is limited to posthospital major organ damage; a subset of postacute

sequelae of SARS-CoV-2 infection (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study).

This manuscript is based on a living review conducted for the Department of Veterans Affairs (VA) Evidence Synthesis Programme (ESP). The full review, now finalised, is available at: https://www.hsrd.research.va.gov/publications/esp/covid-organ-damage.cfm.

METHODS

This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards. For the initial ESP living review (December 2020) and first update (June 2021), we included studies of adults hospitalised for *or with* laboratory confirmed COVID-19. We prioritised postacute major organ damage of greatest clinical relevance. We defined postacute to include major organ damage reported at discharge or any time postdischarge. We included studies reporting relevant symptoms (such as dyspnoea), laboratory data or radiologic studies consistent with presence of a disease. We excluded studies reporting only general symptoms or studies reporting only mean/median values. For September 2021 (final) update, we reported outcomes postdischarge and limited to studies with ≥50 COVID-19 patients.

We focus this manuscript on major organ damage from studies with at least 50 COVID-19 cases and any non-COVID-19 controls. In all studies, cases were hospitalised for COVID-19 (ie, none were hospitalised for another condition with a subsequent positive test for SARS-CoV-2).

Data sources and searches

We searched MEDLINE, Embase and the Cochrane Library from 1 January 2019 to 19 May 2021. The search strategy (online supplemental table 1) was developed with input from expert medical librarians. We reviewed non-peer-reviewed public postings about post-COVID-19 complications for links to peer-reviewed data reports.

Study selection

Consistent with rapid review methods, abstracts were reviewed by one investigator. A subset of 200 abstracts underwent dual independent review with substantial agreement between the two investigators. All articles identified as potentially eligible based on abstract review were independently reviewed by two investigators at the full-text level. Reasons for exclusion were noted. Conflicts

Table 1 Study eligibility criteria

Study characteristic	Include	Exclude
Population	Adults (age 18 and older); at least 50 case patients for manuscript	Children or adolescents, age <18; MERS; SARS
Intervention	Discharge from hospitalisation after admission with or for proven COVID-19*	Data only collected from patients during ongoing hospital acute care admission with or for proven COVID-19
Comparator	Discharge from hospitalisation for individuals without COVID-19 (ideally another respiratory condition); a comparator was not required for the living review but only studies with a control group are included in the manuscript	Not applicable
Outcomes	Prevalence and severity of major organ damage (respiratory, renal, cardiovascular, haematological, neurological and cognitive, endocrine, gastrointestinal and haematologic); healthcare or service use needs related to major organ damage†	No outcomes of interest
Timing	Short-term (<3 months) and long-term (≥3 months) postdischarge	Not applicable
Setting	Any postdischarge setting (eg, home, rehabilitation or long-term care facility); may include rehospitalisation	Not applicable
Study designs	Cohort, case series, other observational; may prioritise articles using a best-evidence approach	Case report, narrative review, descriptive/opinion article with no data

*In the original and first update of the living review, we reported outcomes at the time of discharge. For the September 2021 update and this manuscript, patients must be discharged with postdischarge outcome data available.
†In the original version of the living review, we included studies reporting 'repositive' RT-PCR test results following discharge. For the June 2021 update and later versions, we excluded studies only reporting 'repositive' test results and removed those studies from the original set of included studies. As more information about the natural history of SARS-CoV-2 has become available, it has been recognised that patients may be PCR positive for prolonged periods after an initial COVID-19 illness, and an isolated PCR positivity in such patients (especially for the first 90 days after diagnosis) does not by itself reflect a new infection. Healthcare or service use needs outcomes are not reported in the manuscript.
MERS, Middle East respiratory syndrome.

were resolved by discussion. Inclusion and exclusion criteria are reported in table 1.

Data extraction and quality assessment

Study characteristics (location, design, funding), inclusion and exclusion criteria, baseline demographic data (age, sex, race, comorbidities), hospitalisation characteristics (COVID-19 severity, ICU admission, mechanical ventilation, length of hospital stay), length of time posthospital and outcomes were extracted by one investigator and verified by a second. Discrepancies were resolved by discussion.

We assessed study quality using the Joanna Briggs Institute Appraisal Checklist for Cohort Studies[16] taking into account similarity between groups, assessment of the exposure and outcomes, adjustment for confounding factors and completeness of follow-up.

Data synthesis and analysis

Due to heterogeneity in populations, study designs and methods of outcome assessment, we were unable to pool outcomes data. We narratively synthesised the evidence.

Patient and public involvement

Neither patients nor the public were involved in this research.

Role of the funding source

This review is based on a living rapid review (final version completed) conducted for the VA ESP and funded by the Veterans Health Administration Office of Research and Development, Health Services Research and Development Service. The funding source assigned the topic but was not involved in the study design, data collection, analysis, manuscript preparation or submission.

RESULTS

Overview of studies

Our literature search and study selection process are depicted in figure 1. From the 124 eligible references, 9 included controls.[17–25] Study inclusion and exclusion criteria, patient demographics, COVID-19 and hospitalisation characteristics are reported in online supplemental table 2.

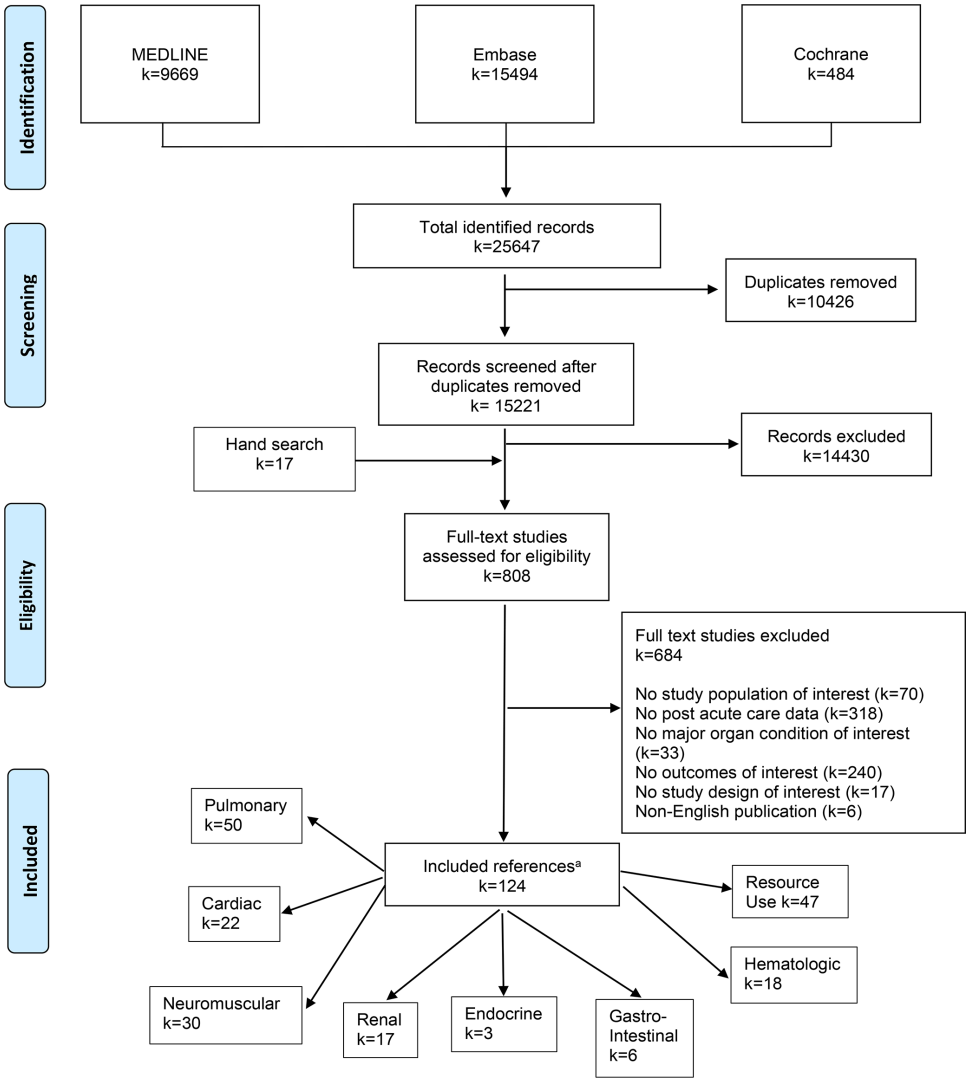

Figure 1 Literature flow diagram.[a]Studies may have reported more than 1 category of outcomes.

In seven of the nine studies, controls were required to have either no positive COVID-19 test, diagnosis or hospital admission for COVID-19,[19–21 23] been quarantined at home for at least 3 months prior to study enrollment,[25] or been a patient in 2019 prior to COVID-19.[17 24] Four studies included hospitalised controls,[17 19 21 24] three included non-hospitalised controls[18 23 25] and two were unclear.[20 22] Six studies created matched COVID-19 and control groups, matching on age, sex, race/ethnicity, geographic location, prior patient encounters and comorbidities (online supplemental table 2).[17–20 22 23] One study adjusted for demographic and comorbidity factors[21] and one recruited volunteers with 'similar demographic characteristics'.[25]

A total of 109 591 COVID-19 patients and 127 089 controls were enrolled. Four studies used administrative databases (three from the USA and one from the UK) with sample sizes ranging from 13 654 to 47 780 COVID-19 patients.[17–20] The other five studies (two from the UK and one each from the USA, Germany and China) enrolled from 58 to 1877 COVID-19 patients.[21–25] Five studies reported outcomes (online supplemental table 3) for multiple organ systems[17–20 23] while four focused on a single system—cardiovascular,[22 25] renal[21] or haematological.[24]

In five studies reporting age, mean or median age ranged from 49 to 70 years.[17 22 23 25] The percentage of males, reported in six studies, ranged from 46% to 94%.[17–19 22–25] There were no statistically significant differences between COVID-19 and control groups for age or sex in any study.

Race was reported in five studies. In a study of US Veterans, 58% of the COVID-19 group and 73% of the seasonal influenza control group were White.[17] In a UK study, 78% of the COVID-19 group and 97% of community-based controls were White.[23] In a US study, 41% of the COVID-19 group and 75% of the non-COVID-19 group were White.[21] In two other studies reporting race, the COVID-19 and control groups were similar.[18 19]

None of the large database studies reported on COVID-19 severity. Among the other five studies, one identified the hospitalised subgroup as having severe COVID-19.[22] One study included only patients with moderate to severe COVID-19[23] while in another, 39% were identified as severe or critical.[25] The percentage of COVID-19 patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation ranged from 6% to 29% (k=3).

Study quality assessments are reported in online supplemental table 4. Only two studies recruited COVID-19 and control patients from the same populations (ie, concurrent, hospitalised patients).[19 21] All but two[24 25] dealt with potential confounders using matching or adjusted analyses. In most studies, the outcome of interest was a new, post-COVID-19 event. In the database studies, events were identified with International Classification of Diseases version 10 (ICD-10) codes while the smaller studies used laboratory testing, imaging or self-report. Follow-up ranged from 48 to 150 days. Most studies provided reasons for incomplete follow-up via a patient flow diagram.

Respiratory disease

Five studies provided pulmonary outcomes (online supplemental table 3).[17–20 23] Two reported on baseline COPD or current smoking status with 5%–14% of COVID-19 patients (0%–12% of controls) having COPD and 8%–35% of COVID-19 patients (8%–23% of controls) being current smokers.

Three large database studies reported incident respiratory disease. A UK study reported that patients with COVID-19, at 146 days postdischarge, had significantly higher new onset respiratory disease (ICD-10 codes J00-99) (22% (6085/28 335)) compared with general population, non-hospitalised controls (0.8% (240/28 335); p<0.001).[18] A US study, with over 54 000 records, reported a significantly increased odds for new onset pneumonia at 1–30 days postdischarge in the COVID-19 group versus hospitalised non-COVID controls (OR 5.5 (95% CI 4.1 to 7.5)).[19] The difference was no longer statistically significant at 31–60, 61–90 and 91–120 days postdischarge. Similarly, patients with COVID-19 were more likely to have 'respiratory failure, insufficiency or arrest' at 0–30 days postdischarge as compared with non-COVID controls (OR 3.3 (95% CI 2.6 to 4.1)), but not at later follow-up. A US study, with over 36 000 records, reported a higher incidence of the combined outcome of 'overall respiratory failure at 4 months after acute illness' in the COVID-19 group (2.6%) compared with non-COVID controls (0.2%) (p<0.001).[20] A higher incidence in the non-COVID-19 group was also noted for acute respiratory failure, chronic respiratory failure and interstitial lung disease.

Only one study reported pulmonary function tests and found no statistically significant difference among COVID-19 cases (n=56) and non-hospitalised, non-COVID controls (n=30) in the percentage of individuals having an abnormal (<80% predicted) forced expiratory volume in 1 s (11% COVID-19, 0.4% control; p=0.42) or forced vital capacity (13% COVID-19, 0% control; p=0.09) at 48 days postdischarge.[23]

Measures of dyspnoea were reported in two studies. Shortness of breath was greater in hospitalised US Veterans with COVID-19 (n=13 654) compared with historical controls hospitalised for seasonal influenza (n=13 997) (HR 1.14 (95% CI 1.04 to 1.26); excess burden per 1000 hospitalised at 6 months: 13.2 (95% CI 3.7 to 21.9)).[17] In another study 'significant breathlessness' based on the mMRC dyspnoea scale (https://mrc.ukri.org/research/facilities-and-resources-for-researchers/mrc-scales/mrc-dyspnoea-scale-mrc-breathlessness-scale/) was reported in 36/56 (64%) COVID-19 patients compared with 3/29 (10%) non-hospitalised, non-COVID cases at 48 days postdischarge.[23]

Cardiovascular outcomes

Five studies reported cardiovascular outcomes (online supplemental table 3).[17 18 20 22 25] Two reported presence of cardiovascular disease at baseline (3%–13% of COVID-19 patients, 5%–16% of controls) and three reported hypertension at baseline (15%–52% of COVID-19 patients, 17%–52% of controls).

Three large database studies reported diagnoses of cardiovascular disease following hospitalisation for COVID-19. The study of over 27 000 Veterans reported greater incident acute coronary disease (HR 1.3 (95% CI 1.1 to 1.5)) and heart failure (HR 1.2 (95% CI 1.03 to 1.4))) for the COVID-19 group versus historical controls hospitalised with seasonal influenza during the 6 months following hospitalisation.[17]

A second study from the USA, including over 36 000 individuals in COVID-19 and concurrent non-COVID control groups, reported new cardiac diagnoses over 4 months follow-up.[20] Coronary disease (including myocardial infarction, acute coronary syndrome and cardiogenic shock) was reported in 1.1% of the COVID-19 group and 0.2% of controls (p<0.001). Congestive heart failure was reported in 1.5% of the COVID-19 group and 0.2% of controls (p<0.001). Myocarditis incidence was rare and the difference between groups was not statistically significant (COVID-19: 0.09%, Control: 0.01%; p=1.0).

A study from the UK reported major adverse cardiovascular events defined as heart failure, myocardial infarction, stroke and arrhythmia, during a mean of 146 days postdischarge.[18] New events were reported in 2.6% (945/36 130) of the COVID-19 group and 0.5% (190/36 130) of the general population control group (p<0.001).

One smaller study used echocardiography to assess left ventricular ejection fraction at 48 days postdischarge.[23] Left ventricular function was normal and comparable between the COVID-19 group and a community-dwelling, non-COVID group.

Two studies used cardiovascular MRI (CMR) to assess myocardial injury. In a study from Germany, 100 patients (33 of whom had been hospitalised) were assessed at a median of 71 days following diagnosis.[22] Late gadolinium enhancement (LGE), reflecting scarring, was observed in 32% (32/100) (myocardial) and 22% (22/100) (pericardial) of the COVID-19 group. Myocardial LGE was significantly more prevalent (p<0.05) in COVID-19 patients than in healthy controls (0%) or risk factor-matched controls (17% (9/57)). Pericardial LGE was significantly more prevalent (p<0.05) in COVID-19 patients than in healthy controls (0%) but not risk factor-matched controls (14% (8/57)).

A second study assessed outcomes at a median of 48 days postdischarge. LGE (myocarditis pattern) was observed in 12% (6/52) of the COVID-19 group (moderate to severe disease) and 7% (2/28) of community-dwelling, non-COVID controls (p=0.47).

The studies also reported on presence of pericardial effusion based on CMR. The study from Germany reported pericardial effusion (>10 mm) in 20% (20/100) of COVID-19 patients, 0% of healthy controls, and 7% (4/57) of risk factor-matched controls (p<0.05 for the COVID-19 group vs each control group) at a median of 71 days following diagnosis.[22] The other study reported pericardial effusion (>10 mm) in 2% (1/52) of the COVID-19 group and 0% (0/28) of community-dwelling, non-COVID controls at a median of 48 days postdischarge.[23]

The CMR study from Germany[22] reported detectable high-sensitivity troponin T (hsTNT) (>3 pg/mL) in 71% (71/100) of the COVID-19 group, with significantly elevated hsTNT (>13.9 pg/mL) in 5% (5/100) at a median of 71 days following diagnosis. The percentage of patients with detectable hsTNT was significantly higher (p<0.05) in the COVID-19 group than in healthy (22% (11/50) or risk factor-matched controls (54% (31/57)). The second study, with a control group of non-COVID-19 community members reported no cases of abnormal troponin T in either the COVID-19 or control groups at a median of 48 days postdischarge.[23]

Neurologic and cognitive outcomes

Neurologic and cognitive outcomes were reported by four studies (online supplemental table 3).[17 19 20 23]

The study of over 27 000 US Veterans reported an increased risk of stroke 6 months after hospitalisation for COVID-19 among individuals without a history of stroke in the past year, as compared with historical, matched controls with seasonal influenza (HR 1.30; 95% CI 1.05 to 1.60).[17] Another US study reported the prevalence of new onset stroke during the 4 months posthospitalisation.[20] Ischaemic and haemorrhagic stroke was reported in 1.1% of the COVID-19 group and 0.3% of matched non-COVID controls (risk difference 0.8% (95% CI 0.4 to 1.2), p<0.001).

For incident neurocognitive disorders, US Veterans hospitalised for COVID-19 had an excess burden per 1000 COVID-19 persons at 6 months of 16.2 (95% CI 10.4 to 21.2) compared with hospitalised seasonal influenza cases.[17] In another database study, neurocognitive disorders, defined using the Clinical Classification Software Refined categories, were more likely in patients hospitalised with COVID-19 versus non-COVID controls (OR 1.6 (95% CI 1.2 to 2.1)) in the first 30 days after discharge but not at 60, 90, or 120 days.[19]

In a US database study enrolling adults age 18–65 years, newly diagnosed dementia through 120 days postacute infection was greater in the COVID-19 group compared with non-COVID controls (0.2% vs 0.03%; risk difference 0.2% (95% CI 0.7 to 0.3), p<0.001).[20] In the same study, Alzheimer-type dementia was noted in 0.04% of the COVID-19 group and 0% of controls (p<0.001).

One study reported Montreal Cognitive Assessment (MoCA) scores of less than 26 (ie, cognitive impairment) in 28% of the COVID-19 group and 17% of community-based controls (p=0.30) at a median of 48 days postdischarge.[23]

Renal outcomes

Renal outcomes were reported by six studies (online supplemental table 3).[17–21 23] A history of chronic kidney disease (CKD) at baseline, reported in two studies, was noted in 13% of patients in both the COVID-19 and the control groups in one study[18] and 33% of the COVID-19 group and 35% of controls in the other.[21]

CKD post-COVID-19, identified by ICD-10 codes, was reported in three large database studies.[17 18 20] In the study of US Veterans, the HR for a new diagnosis of CKD during the 6 months after acute infection in the COVID-19 group

vs seasonal influenza controls was 1.4 (95% CI 1.1 to 1.7).[17] A second US study, with data from over 36000 individuals, reported new diagnoses of CKD (all stages) at 4 months after acute illness in 2.1% of the COVID-19 group and 0.7% of non-COVID controls (p<0.001).[20] The third study, completed in the UK, included data from over 82000 individuals and reported new onset CKD stages 3–5 in 0.6% of the COVID-19 group and 0.3% of general population controls at a mean of approximately 146 days postdischarge.[18]

A new diagnosis of acute kidney injury (AKI) following discharge was reported in three large database studies.[17 19 20] The study of US Veterans reported an adjusted HR for AKI during the 6 months following COVID-19 infection for the COVID-19 group vs seasonal influenza controls (HR 1.2 (95% CI 1.1 to 1.4)).[17] A second US study reported ORs for 'acute and unspecified kidney failure' versus hospitalised non-COVID-19 controls.[19] ORs decreased from 1.3 (95% CI 1.0 to 1.6) at 30 days postdischarge to 0.6 (95% CI 0.4 to 0.8) at 120 days postdischarge. The third study, also from the USA, reported a new diagnosis of AKI during the 4 months after acute infection in 2.9% of the COVID-19 group and 0.5% of non-COVID controls (p<0.001).[20]

In a study of patients with COVID-19-associated AKI, defined as >50% increase in creatinine over baseline or 0.3 mg/dL increase over lowest level at 48 hours, and a control group with non-COVID associated AKI, the COVID-19 group demonstrated lower rates of AKI recovery post hospital discharge (HR_{adj} 0.57 (95% CI 0.35 to 0.92); p=0.02).[21]

Endocrine

Three database studies, two from the USA[17 20] and one from the UK,[18] reported the presence of diabetes (online supplemental table 3). Diabetes at baseline was reported in one study (24%).[18] A US study, with data from over 27000 Veterans without a history of diabetes in the previous year, reported greater risk for diabetes in the COVID-19 group than in a matched, seasonal influenza control group (HR 1.6 (95% CI 1.4 to 1.9)).[17] The excess burden per 1000 hospitalised COVID-19 patients was 21.4 (95% CI 15.1 to 26.8) at 6 months following COVID-19 infection. The second US study included over 36000 hospitalised patients in COVID-19 and matched non-COVID-19 groups. Through 4 months after acute illness, a new clinical diagnoses of type 2 diabetes was reported in 3% of the COVID-19 group and 0.8% of controls (risk difference 2.2% (95% CI 1.4 to 3.2)).[20]

The UK study, with data from over 72000 individuals (COVID-19 and matched, general population controls) reported new onset type 1 diabetes, during a mean of approximately 146 days after discharge, in 1.1% (400/36 100) of the COVID-19 group and 0.3% (125/36 100) of controls.[18] Rates per 1000 person-years were 28.7 for the COVID-19 group and 8.2 for controls.

Gastrointestinal outcomes

Three studies reported gastrointestinal outcomes (online supplemental table 3).[17 18 20] Two database studies identified gastrointestinal disease using ICD-10 codes.[17 18] The study of Veterans identified incidence of gastrointestinal disorders (eg, dysphagia) in over 27000 individuals hospitalised for either COVID-19 or seasonal influenza.[17] During 6 months follow-up, the excess burden per 1000 COVID-19 persons was 19.3 (95% CI 12.8 to 25.1). The second study, from the UK (46395 matched pairs), identified new onset chronic liver disease over a mean follow-up of 140 days among individuals hospitalised with COVID-19 (0.2% (70/46 395)) compared with a non-hospitalised general population (0.04% (15/46 395)).[18] The difference was statistically significant (p<0.001). The third study, enrolling over 18000 matched pairs, reported liver test abnormalities at 4 months after acute illness in 3.3% of the COVID-19 group and 1.4% of the control group (p<0.001).[20]

Haematological outcomes

Three studies reported venous thromboembolism outcomes postdischarge (online supplemental table 3).[17 19 20] A US study, including data from over 54000 individuals, reported ORs for acute pulmonary embolism (PE) versus non-COVID controls of 1.5 (95% CI 1.0 to 2.1) at 30 days postdischarge and 1.4 (95% CI 0.9 to 2.1) at 60 days. ORs at 90 and 120 days were also not statistically significant.[19] Another US study, with data from over 36000 individuals, reported PE in 1.3% of the COVID-19 group and 0.1% of the non-COVID controls through 120 days postinfection.[20] Deep venous thrombosis was reported in 2.3% of the COVID-19 group and 0.3% of controls. The study of over 27000 US Veterans observed an excess burden for PE per 1000 COVID-19 persons (vs seasonal influenza controls) of 18.3 (95% CI 15.8 to 20.3) and an HR for thromboembolism of 2.3 (95% CI 1.9 to 2.6) through 150 days postdischarge.[17]

The same studies reported coagulation disorders (with varying definitions of 'coagulation' between studies). The study of over 27000 US Veterans reported an excess burden of coagulation (defined by ICD-10 codes, not specified) per 1000 COVID-19 persons of 14.3 (95% CI 10.1 to 17.9) compared with seasonal influenza controls.[17] Another US study reported a higher risk of hypercoagulability (ICD-10 codes D68 and I82) in the COVID-19 group (3.2%) than in non-COVID controls (0.4%) during the 4 months after acute illness.[20] The risk difference was 2.8% (95% CI 2.3% to 3.6%) (p<0.001). The third study, also from the USA, reported odds ratios (COVID-19 vs hospitalised non-COVID-19 controls) for the overall category of coagulation and haemorrhagic disorders.[19] The ORs at 30, 60, 90 and 120 days were 1.3 (95% CI 1.0 to 1.6), 1.3 (95% CI 0.95 to 1.7), 0.65 (95% CI 0.5 to 0.9) and 0.66 (95% CI 0.5 to 0.97), respectively. It was noted that the top five coagulation and haemorrhagic disorders were 'unspecified thrombocytopenia, other primary thrombophilia, other secondary thrombocytopenia, unspecified coagulation defect and other thrombophilia'.

CONCLUSIONS

Key findings

Our review of COVID-19 postacute major organ damage found that incident respiratory disease may be higher in

posthospitalisation COVID-19 cases as compared with non-COVID controls. Prevalence ranged from 2% to 22% in COVID-19 groups compared with less than 1% in controls. Dyspnoea was much more prevalent (64% vs 10%) and there was greater risk for dyspnoea in COVID-19 groups than in controls.

Patients with COVID-19 were also at greater risk for incident cardiovascular disease outcomes (including acute myocardial infraction, coronary disease and heart failure) compared with controls. Prevalence of new cardiovascular events ranged from approximately 1% to 3% in the COVID-19 groups and less than 1% in controls. One large database study reported that a clinical diagnosis of myocarditis based on ICD-10 codes was rare and did not differ between those with COVID-19 and controls (0.09% vs 0.01%; p=1.0). However, two small studies used MRI to assess prevalence of myocarditis based on LGE patterns. One specifically excluded individuals with active cardiac symptoms and the other did not require symptoms to proceed to MRI. LGE based 'myocarditis' in these two studies was much higher compared with the database report and was noted in 12% vs 7% (p=0.47) and 32 vs 17% (p<0.05) of COVID-19 patients and controls, respectively.

Among other organ systems, the prevalence of, or risk for, stroke, new-onset CKD, acute kidney injury, new-onset diabetes, incident gastrointestinal disorders and new-onset chronic liver disease was higher in COVID-19 groups than in matched controls. The incidence of dementia post-COVID-19 was low but may exceed that of non-COVID cases. The prevalence of, or risk for, coagulation and haemorrhagic disorders was higher in COVID-19 groups than in control groups though disorder definitions were unclear and varied.

Limitations of the evidence exist. Although evidence includes four large database studies with controls, most data, cited in the living review, are from small single centre convenience sample studies with poorly described populations or measures of major organ damage. Among the nine studies with controls cited in this manuscript, control groups varied. Three studies included historical controls and six included concurrent controls. In four of the concurrent control studies, control group patients were not hospitalised. Reported prevalence rates are likely highly dependent on pre-existent demographics and comorbidities of the study population, COVID-19 disease severity, the measures used to assess and define major organ damage and the timing of assessment relative to hospital discharge. Follow-up times for the nine studies with control groups ranged from 30 to 150 days; only one study reported outcomes at multiple time points post-COVID. Long-term major organ damage (ie, ≥6 months) prevalence and duration of major organ damage remain unknown. There are no data reporting on outcomes based on patient living situation prior to COVID-19 infection (ie, community dwelling vs nursing home or assisted care centres). No data exist to ascertain if outcomes differ based on treatments received for COVID-19, COVID-19 vaccination status or infection with different COVID-19 variants. Disease diagnosis relied on clinician coding rather than a standardised physiologic/laboratory value. There are also limitations of our review methods. We defined 'postacute COVID-19' as posthospital discharge. The applicability of these findings to non-hospitalised patients with acute COVID-19 symptoms is unclear.

We are aware of several systematic reviews reporting persistent symptoms following recovery from acute COVID-19.[26–30] Fatigue, dyspnoea, chest pain, sleep disorders, cognitive impairment and difficulty concentrating are commonly reported symptoms. Our review complements these reviews by focusing on (1) patients requiring hospitalisation for laboratory-confirmed COVID-19, (2) major organ damage from all organ systems rather than symptoms and (3) controlled studies.

In conclusion, postacute COVID-19 major organ damage following hospitalisation for COVID-19 infection is common and likely higher than non-COVID controls. However, there is substantial uncertainty due to evidence limitations. More consistent reporting of clinically relevant outcomes and pre-COVID-19 health status as well as use of appropriately matched controls is needed to address evidence gaps.

Author affiliations
[1]Center for Care Delivery and Outcomes Research, Minneapolis VA Health Care System, Minneapolis, MN, USA
[2]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA
[3]Division of Cardiology, Minneapolis VA Health Care System, Minneapolis, MN, USA
[4]Section of Endocrinology and Metabolism, Department of Medicine,Minneapolis VA Health Care System, Minneapolis, MN, USA
[5]General Internal Medicine, Minneapolis VA Health Care System, Minneapolis, MN, USA
[6]Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA
[7]Section of Infectious Diseases, Minneapolis VA Health Care System, Minneapolis, MN, USA
[8]Hematology/Oncology Section, Minneapolis VA Health Care System, Minneapolis, MN, USA
[9]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Minneapolis VA Health Care System, Minneapolis, MN, USA
[10]Division of Nephrology, Minneapolis VA Health Care System, Minneapolis, MN, USA
[11]Division of Gastroenterology, Minneapolis VA Health Care System, Minneapolis, MN, USA
[12]Division of Geriatrics, Hennepin Healthcare, Minneapolis, Minnesota, USA
[13]Geriatric Research, Education, and Clinical Center, Minneapolis VA Health Care System, Minneapolis, MN, USA
[14]Department of Pharmacy, Minneapolis VA Health Care System, Minneapolis, MN, USA
[15]Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, MN, USA

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ORCID iD

Nancy Greer http://orcid.org/0000-0002-8898-6868

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Supplemental Table 1. MEDLINE/EMBASE Search Strategy

1	(coronavir* or corona virus* or betacoronavir* or covid19 or covid 19 or nCoV or CoV 2 or CoV2 or sarscov2 **SARS 2 or SARS-CoV-2** or 2019nCoV or 2019 novel coronavirus* or 2019 novel CoV or wuhan virus* or ((wuhan or hubei or huanan) and (severe acute respiratory or pneumonia*))).ti,ab,kw.
2	Coronavirus Infections/ or Coronavirus/ or betacoronavirus/
3	1 or 2
4	Pulmonary fibrosis.ti,ab,kw. or exp Pulmonary Fibrosis/
5	exp Lung Diseases, Obstructive/
6	4 or 5
7	acute kidney injury.ti,ab,kw. or exp Acute Kidney Injury/
8	exp Renal Insufficiency, Chronic/
9	(end stage renal disease or ESRD or AKI or CKD).ti,ab,kw.
10	7 or 8 or 9
11	myocardial infarction.ti,ab,kw. or exp Myocardial Infarction/
12	(heart attack or heart failure or MI).ti,ab,kw.
13	myocarditis.ti,ab,kw. or exp Myocarditis/
14	exp Arrhythmias, Cardiac/
15	arrhythmia*.ti,ab,kw.
16	11 or 12 or 14 or 14 or 15
17	exp Venous Thrombosis/
18	exp Pulmonary Embolism/ or exp Venous Thromboembolism/
19	(deep ve* thrombosis or DVT or pulmonary embolism or PE).ti,ab,kw.
20	anemia.ti,ab,kw. or exp Anemia/
21	17 or 18 or 19 or 20
22	stroke.ti,ab,kw. or exp Stroke/
23	exp Cognitive Dysfunction/
24	exp Confusion/
25	exp Seizures/
26	exp Headache/
27	(stroke* or cerebrovascular accident* or cognitive impairment or cognitive dysfunction or delirium or confusion or seizure* or headache*).ti,ab,kw.
28	22 or 23 or 24 or 25 or 26 or 27
29	exp Diabetes Mellitus/
30	diabetes.ti,ab,kw.
31	29 or 30
32	exp Hepatitis/
33	exp Colitis/
34	(hepatitis or hepatocellular injur* or colitis).ti,ab,kw.
35	32 or 33 or 34
36	"Autoimmune Diseases of the Nervous System"/
37	autoimmune disease*.ti,ab,kw.
38	Musculoskeletal Diseases/
39	musculoskeletal.ti,ab,kw.
40	36 or 37 or 38 or 39
41	6 or 10 or 16 or 21 or 28 or 31 or 35 or 40
42	exp Hospitalization/ or exp Intensive Care Units/ or Inpatients/ or Subacute Care/
43	(hospital or hospitalized or hospitalization or intensive or ICU or care or post?acute or inpatient or inpatients or admit or admitted or admitting).ti,ab,kw.
44	42 or 43
45	3 and 41 and 44
46	limit 45 to english language
47	limit 46 to yr="2019 -Current"

Supplemental Table 2. Study Characteristics for Studies with Control Groups

Author, Year Country Study Design Funding	Inclusion/Exclusion Criteria	Baseline Demographic Data	Hospitalization Characteristics Time of Post-hospital Follow-up
Al-Aly, 2021(1) USA (Veterans) Retrospective Funding: VA	Inclusion: Admitted for COVID-19 within 30 days after or 5 days before first positive test and survived at least 30 days after hospital admission; selected from 98,661 patients with positive COVID-19 test between March 01, 2020 and November 30, 2020 Exclusion: None specified Controls: hospitalized for seasonal influenza between October 01, 2016 and February 29, 2020; survived 30 days after hospital admission Propensity scores based on predefined variables were estimated to adjust for potential confounders	N=13,654 (COVID-19 group); N=13,997 (Control group) Age (years, mean): 70 (COVID-19 and Control groups) Gender (% male): 94 (COVID-19 and Control groups) Race/ethnicity: COVID-19 group: White 59%, Black 34%; Control group: White 73%, Black 22% Comorbidities: NR	COVID-19 severity: NR ICU admission: 26% (n=3586) Respiratory support Mechanical ventilation or ECMO: NR NIV, HFNC, or CPAP: NR Other: NR Length of hospital stay: NR Planned time post-hospital in patients that survived 30 days after diagnosis (days): 180 Reported time post-hospital (days, median): COVID-19 group: 150, Control group: 157
Ayoubkhani, 2021(2) United Kingdom Retrospective Funding: none	Inclusion: Hospitalized for COVID-19, (positive laboratory test or clinical diagnoses) from January 1, 2020 to end of August 2020 Exclusion: Not discharged alive by August 31, 2020 or birth date or gender unknown Controls: individuals in general population, did not meet inclusion criteria for COVID-19, and had not died before January 1, 2020; 79% had prior hospital admission	N=47,780 (for both COVID-19 group and matched control group) Age (%): COVID-19 group Age <30: 5; 30-49: 16; 50-69: 33; ≥70: 46 Control group <30: 3; 30-49: 19; 50-69: 33; ≥70: 46 Gender (% male): 55 (COVID-19 and Control groups) Race/ethnicity: White 72%, Asian 9%, Black 5% (COVID-19 and Control groups) Comorbidities:	COVID-19 severity: NR ICU admission: 10% (n=4745) Respiratory support: NR Length of hospital stay: NR Planned time post-hospital: NR Reported time post-hospital (days, mean): COVID-19 group: 140, Control group: 153

Author, Year Country Study Design Funding	Inclusion/Exclusion Criteria	Baseline Demographic Data	Hospitalization Characteristics Time of Post-hospital Follow-up
	Patients and controls matched (1:1) on several confounding variables; all were active patients in National Health Service	MACE: 24% (COVID-19 and Control groups) CKD: !3% (COVID-19 and Control groups) COPD: COVID-19 group: 14%; Control group: 12% DM: 24% (COVID-19 and Control groups) HTN: 52% (COVID-19 and Control groups) Obesity (BMI ≥30): 32% (COVID-19 and Control groups) Smoking: 8% current, 41% former (COVID-19 and Control groups)	
Chevinsky 2021(3) USA Retrospective Funding: Not reported	Inclusion: Hospitalized for COVID-19 (ICD-10 code) from March 1 to June 30, 2020 Exclusion: Patients with at least 1 encounter preceding index encounter or who died or were pregnant in index encounter Controls: hospitalized individuals who did not meet inclusion criteria for COVID-19 and were not diagnosed with COVID-19 during the 4 months after index encounter Patients and controls matched (1:1) based on propensity scores on several confounding variables	N=27,284 adults for both COVID-19 and Control groups Age (%): COVID-19 group Age 18-39: 9; 40-49: 10; 50-64: 28; ≥65: 53 Control group Age 18-39: 11; 40-49: 9; 50-64: 27; ≥65: 54 Gender (% male): COVID-19 group: 48; Control group: 47 Race/ethnicity: COVID-19 group: White 48%, Black 26%, Asian 2%, Hispanic 13% Control group: White 47%, Black 26%, Asian 2%, Hispanic 14% Comorbidities: NR	COVID-19 severity: NR ICU admission: both groups 40% Respiratory support: NR Length of hospital stay (days, median): COVID-19 group 6 (range 3, 11); Control group 4 (range 2, 6) Planned time post-hospital (days): 30-120 Reported time post-hospital (days): NR
Daugherty 2021(4) USA	Inclusion: Ages 18-65 diagnosed with COVID-19 (SARS-CoV-2); continuous enrollment in the health plan from January	N=21,746 hospitalized (N=18,118 for both COVID-19 and control groups in matched analysis after	COVID-19 severity: NR ICU admission: 13% (n=2933)

Author, Year Country Study Design Funding	Inclusion/Exclusion Criteria	Baseline Demographic Data	Hospitalization Characteristics Time of Post-hospital Follow-up
Retrospective Funding: Insurance (Research & Development)	1, 2019 to index date (defined by first of: 1) primary, secondary, or tertiary diagnosis of COVD-19; 2) administrative claims with ICD-10 codes U07.1 or either B34.2 or B97.29 before April 1, 2020; 3) documentation of positive PCR test in outpatient laboratory dataset; or 4) admitted to hospital for COVID-19 (based on diagnostic code)) Exclusion: Positive SARS-CoV-2 antibodies but without documented infection; ICD-10 codes B34.2 or B97.29 on or after April 1, 2020; and admitted to hospital for suspected COVID-19 but missing diagnostic codes Controls: ages 18-65 without COVID-19 (SARS-CoV-2) diagnosis with continuous health plan enrollment from January 1 2019 to randomly assigned month and day drawn from the SARS-CoV-2 infection group (2020 comparator group used for analysis of hospitalized patients) Patients and controls matched (1:1) using propensity scores based on 108 variables	exclusion if less than index date + 21 days of follow-up); demographics and comorbidities NR for hospitalized subgroup Age (years, mean): NR Gender (% male): NR Race/ethnicity: NR Comorbidities: NR	Respiratory support: NR Length of hospital stay: NR Planned time post-acute infection* (days): 90-180 Reported time post-acute infection* (days, mean): 120 NOTE: post-acute infection defined as index date plus 21 days
Nugent, 2021(5) USA Retrospective Funding: Foundation	Inclusion: Tested for COVID-19 by RT-PCR, developed AKI during hospitalization, survived past discharge, did not require dialysis within 3 days of discharge, had ≥1 measurement of serum creatinine as an outpatient post-discharge	N=1612 (182 COVID-19) Age (years, median): 70 (67 COVID-19 group) Gender (% male): 50 (53 COVID-19 group) Race/ethnicity: 40% Black, 41% White, 3% Asian, 17% Other; 22% Hispanic (COVID-19 group)	COVID-19 severity: NR ICU admission: 37% (COVID-19 group) Respiratory support Mechanical ventilation or ECMO: 29% (COVID-19 group)

Author, Year Country Study Design Funding	Inclusion/Exclusion Criteria	Baseline Demographic Data	Hospitalization Characteristics Time of Post-hospital Follow-up
	Exclusion: Age <18 years, determined to have ESKD, received prior kidney transplant, initial creatinine level ≥4 mg/dL Controls: hospitalized patients with AKI and negative test for COVID-19	Comorbidities: CVD: NR CKD: 35% (33% COVID-19 group) COPD: 47% (45% COVID-19 group) DM: 52% (64% COVID-19 group) HTN: 89% Obesity: NR Smoking: NR	NIV, HFNC, or CPAP: NR Other: NR Length of hospital stay (days, mean): 14 (COVID-19 group) Planned time post-hospital: NR Reported time post-hospital (days, median): 93 (COVID-19 group)
Puntmann, 2020(6) Germany Prospective Funding: Government, Industry, Institution	Inclusion: Minimum of 2 weeks post-diagnosis of SARS-CoV-2 by RT-PCR; resolution of respiratory symptoms; negative results on swab test at end of isolation period Exclusion: Recently recovered from COVID-19 and referred for clinical CMR imaging; unwilling to participate; absolute contraindications for contrast-enhanced magnetic resonance study Controls: healthy and risk-factor matched groups	N=100 Age (years, mean): 49 Gender (% male): 53 Race: NR Comorbidities: CVD: 13% CKD: NR COPD: 21% DM: 18% HTN: 22% Obesity: NR Smoking: 22%	COVID-19 severity: 18% asymptomatic, 49% mild/moderate (both recovered at home), 33% severe (required hospitalization) ICU admission: NR Respiratory support Mechanical ventilation or ECMO: 2%, 6% (hospitalized group) NIV, HFNC, or CPAP: 17%, 52% (hospitalized group) Other: 28% (NR for hospitalized group) Length of hospital stay: NR Planned/reported time post-hospital: NR NOTE: median time from diagnosis to CMR was 71 [IQR 64-92] days)

Author, Year Country Study Design Funding	**Inclusion/Exclusion Criteria**	**Baseline Demographic Data**	**Hospitalization Characteristics Time of Post-hospital Follow-up**
Raman, 2021(7) United Kingdom Prospective Funding: Government, Foundation	Inclusion: All patients with moderate to severe laboratory COVID-19 (positive SARS-CoV-2) Exclusion: Severe comorbidities (end-stage renal, cardiac, liver, or neurological disease), contradictions to MRI Controls: uninfected (negative for SARS-CoV-2 and asymptomatic), from the community (not hospitalized), group-matched for age, sex, body mass index, and risk factors	N=58 COVID-19 Age (years, mean): 55 Gender (% male): 59 Race/ethnicity: 22% Black/Asian and minority ethnic groups; 78% White Comorbidities: CAD: 3% CKD: NR COPD: 5% DM: 16% (Type 1 and 2) HTN: 38% Obesity: NR Smoking: 35% Current or ex-smoker	COVID-19 severity: Moderate to severe (inclusion criteria) ICU admission: 36% (21/58) Respiratory support Mechanical ventilation or ECMO: 21% NIV, HFNC, CPAP: 26% Other: 46% Length of hospital stay (days, median): 8.5 Planned time post-hospital (days): 30-180 Reported time post-hospital (days, median): 48
Roberts, 2020(8) United Kingdom Prospective Funding: Not reported	Inclusion: Patients discharged following admission for COVID-19; 6-week follow-up for hospital-associated VTE (HA-VTE) events Exclusion: None reported NOTES: 1) patients received thromboprophylaxis while hospitalized Controls: cohort of post-discharge HA-VTE following medical admission in 2019	N=1877 Age (years, mean): NR Gender (% male): NR Race: NR Comorbidities: NR	COVID-19 severity: NR ICU admission: NR (11% [208/1877] admitted to critical care) Respiratory support: NR Length of hospital stay: NR Planned/reported time post-hospital (days): 90

Author, Year Country Study Design Funding	Inclusion/Exclusion Criteria	Baseline Demographic Data	Hospitalization Characteristics Time of Post-hospital Follow-up
Xiong, 2021(9) China Prospective Funding: Not reported	Inclusion: Ages 20-80 years, diagnosed with COVID-19, cured and discharged Exclusion: Severe and complex underlying diseases, receiving invasive treatment, women who were pregnant or breastfeeding Controls: free of COVID-19, similar demographics, completely quarantined at home for >3 months with little physical work	N=538 (those who completed telephone follow-up from group of 891 discharged) Age (years, median): 52 Gender (% male): 46 Race/ethnicity: NR Comorbidities: CHD: 3% CKD: 2% COPD: 4% DM: 7% HTN: 15% Obesity: NR Smoking: NR	COVID-19 severity: 5% critical, 34% severe, 62% “general” ICU admission: NR Respiratory support: NR Length of hospital stay: NR Planned time post-hospital: NR Reported time post-hospital (days, median): 97

Abbreviations: AKI=acute kidney injury; CAD=coronary artery disease; CKD=chronic kidney disease; CMR=cardiovascular magnetic resonance; COPD=chronic obstructive pulmonary disease; COVID-19=SARS-CoV-2: 2019 novel coronavirus; CPAP=continuous positive airway pressure; CVD=cardiovascular disease: DM=diabetes mellitus; ECMO=extracorporeal membrane oxygenation; ESKD=end stage kidney disease; HFNC=high-flow nasal cannula; HTN=hypertension; ICD=International Classification of Disease; IQR=interquartile range; ICU=intensive care unit; MRI=magnetic resonance imaging; NIV=non-invasive ventilation; NR=not reported; RT-PCR: reverse transcriptase polymerase chain reaction; VTE=venous thromboembolism; WHO=World Health Organization

Supplemental Table 3. Included Studies and Outcomes Reported

Author, year Country Sample Size (COVID-19/ control) Description of Controls	ICU Admission (%) Assessment Time Post-Discharge	Pulmonary Outcomes	Cardio-vascular Outcomes	Neurologic and Cognitive Outcomes	Renal Outcomes	Endocrine Outcomes	Gastro-intestinal Outcomes	Hematologic Outcomes
Al-Aly, 2021(1) USA 13,654/13,997 Historical controls; hospitalized for seasonal Influenza and survived 30 days after admission; propensity scores based on pre-defined variables estimated to adjust for potential confounders	26% COVID-19: 150 days Controls: 157 days (median)	**Shortness of breath** HR (adjusted) 1.14 (95%CI 1.04, 1.26) Excess burden per 1000 hospitalized COVID-19 patients at 6 months 13.22 (95%CI 3.68, 21.94)	**Acute coronary disease**[a] HR (adjusted) 1.29 (95%CI 1.11, 1.50) Excess burden per 1000 hospitalized COVID-19 patients at 6 months 9.36 (95%CI 4.16, 13.86) **Heart Failure**[a] HR (adjusted) 1.19 (95%CI 1.03, 1.39) Excess burden per 1000 hospitalized COVID-19 patients at 6 months 6.31 (95% CI 1.02, 10.88)	**Stroke**[a] HR (adjusted) 1.30 (95%CI 1.05, 1.60) Excess burden per 1000 COVID-19 persons at 6 months 4.79 (95%CI 1, 7.87) **Neuro-cognitive Disorders**[a] Excess burden per 1000 COVID-19 persons at 6 months 16.16 (95%CI 10.40, 21.19) **Memory problems**[a] HR (adjusted) 1.42 (95%CI 1.23, 1.63) Excess burden per 1000	**AKI**[a] HR (adjusted) 1.24 (95%CI 1.10, 1.40) Excess burden per 1000 COVID-19 persons at 6 months 11.21 (95%CI 5.36, 16.43) **CKD**[a] HR (adjusted) 1.35 (95%CI 1.10, 1.65) Excess burden per 1000 COVID-19 persons at 6 months 6.03 (95%CI 2.17, 9.20)	**Diabetes**[a] HR (adjusted) 1.60 (95%CI 1.36, 1.87) Excess burden per 1000 hospitalized COVID-19 patients at 6 months 21.39 (95%CI 15.10, 26.77)	**"Gastro-intestinal Disorders"** (includes dysphagia)[a] Excess burden per 1000 COVID-19 persons 19.28 (95%CI 12.75, 25.13)	**Thrombo-embolism**[a] HR (adjusted) 2.26 (95% CI 1.94, 2.64) 25.74, 33.24) **Pulmonary Embolism**[a] Excess burden per 1000 COVID-19 persons at 6 months 18.31 (95%CI 15.83, 20.25) **Coagulation Disorder**[a] Excess burden per 1000 COVID-19 persons at 6 months 14.31 (95%CI 10.08, 17.89)

Author, year Country Sample Size (COVID-19/ control) Description of Controls	**ICU Admission (%) Assessment Time Post-Discharge**	**Pulmonary Outcomes**	**Cardio-vascular Outcomes**	**Neurologic and Cognitive Outcomes**	**Renal Outcomes**	**Endocrine Outcomes**	**Gastro-intestinal Outcomes**	**Hematologic Outcomes**
				COVID-19 persons at 6 months 16.59 (95%CI 10.59, 21.84)				
Ayoubkhani, 2021(2) United Kingdom 47,780/47,780 Concurrent controls, general population, not meeting inclusion criteria for COVID-19; ≥1 record in general practice database in past year (ie, active patients); matched (1:1) on demographic and comorbidity factors	10% COVID-19: 140 days Controls 153 days (mean)	**Respiratory Disease, new onset events** COVID-19: 21.5% Control: 0.8% P<.001	**MACE, new onset events** COVID-19: 2.6% Control: 0.5% P<.001	**NR**	**CKD, new onset events** COVID-19: 0.6% Control: 0.3%	**Diabetes, new onset events** COVID-19: 1.1% Control: 0.3% P<.001	**Chronic Liver Disease, new onset** COVID-19: 0.2% Control: 0.04% P<.001	**NR**
Chevinsky, 2021(3) USA 27,284/27,284	40% COVID-19/ Controls	**Respiratory failure; insufficiency; arrest**	**NR**	**Neuro-cognitive disorders** 90-120 days after discharge	**Acute and unspecified kidney failure** 90-120 days after discharge	**NR**	**NR**	**Acute Pulmonary Embolism** 90-120 days after discharge

Author, year Country Sample Size (COVID-19/ control) Description of Controls	**ICU Admission (%) Assessment Time Post-Discharge**	**Pulmonary Outcomes**	**Cardio-vascular Outcomes**	**Neurologic and Cognitive Outcomes**	**Renal Outcomes**	**Endocrine Outcomes**	**Gastro-intestinal Outcomes**	**Hematologic Outcomes**
Concurrent controls, hospitalized, did not meet inclusion for COVID-19; no diagnosis of COVID-19 during 4 months after index encounter; matched (1:1) on demographic, comorbidity, and socioeconomic factors	30-120 days (planned)	90-120 days after discharge OR (adjusted) 0.73 (95%CI 0.47, 1.10) **Pneumonia** (except that caused by tuberculosis) 90-120 days after discharge OR (adjusted) 1.00 (95%CI 0.58, 1.90)		OR (adjusted) 1.10 (95%CI 0.72, 1.70)	OR (adjusted) 0.56 (95%CI 0.39, 0.80)			OR (adjusted) 1.2 (95%CI 0.70, 2.10) **Coagulation and Hemorrhagic Disorders** 90-120 days after discharge OR (adjusted) 0.66 (95%CI 0.45, 0.97)
Daugherty, 2021(4) USA 18,118/18,118 Concurrent controls; no clinical diagnosis related to COVID-19, no positive test for SARS-CoV-2,	13% COVID-19/ Controls=120 days (mean)	**New Clinical Diagnoses: Respiratory failure** (acute respiratory failure, chronic respiratory failure, interstitial lung disease) COVID-19: 2.6% Control: 0.2%	**New Diagnoses Coronary disease overall** (MI, acute coronary syndrome, cardiogenic shock) COVID-19: 1.1% Control: 0.2% P<.001	**Stroke** (ischemic and hemorrhagic) COVID-19: 1.1% Control: 0.3% P<.001 **New Clinical Diagnoses Amnesia/ memory difficulty**	**Kidney injury** (acute and chronic) COVID-19: 3.0% Control: 0.8% **Acute kidney injury** COVID-19: 2.9% Control: 0.5% **CKD**	**New Clinical Diagnoses Diabetes** (Type 2) COVID-19: 3.0% Control: 0.8% P<.001	**Liver Test Abnormality** COVID-19: 3.3% Control: 1.4% P<.001	**DVT** COVID-19: 2.3% Control: 0.30% **PE** COVID-19: 1.3% Control: 0.1% P<.001 for all outcomes **Hyper-coagulability** COVID-19: 3.2% Control: 0.4%

Author, year Country Sample Size (COVID-19/ control) Description of Controls	ICU Admission (%) Assessment Time Post-Discharge	Pulmonary Outcomes	Cardio-vascular Outcomes	Neurologic and Cognitive Outcomes	Renal Outcomes	Endocrine Outcomes	Gastro-intestinal Outcomes	Hematologic Outcomes
no hospital admission for COVID-19, continuous health plan enrollment in past year, matched (1:!) on demographic, comorbidity, and provider visit factors		Risk difference 2.4% (95%CI 1.35, 3.20) **Acute respiratory failure** COVID-19: 2.6% Control: 0.18% Risk difference 2.4% (95%CI 1.67, 3.43) **Chronic respiratory failure** COVID-19: 1.5% Control: 0.1% Risk difference 1.5% (95%CI 0.97, 1.75) **Interstitial lung disease** COVID-19: 1.6% Control: 0.1%	**Congestive Heart Failure** COVID-19: 1.5% Control: 0.2% P<.001 **Myocarditis** COVID-19: 0.09% Control: 0.01% P=1.0	COVID-19: 2.9% Control: 0.4% P<.001 **Dementia** COVID-19: 0.2% Control: 0.03% P<.001 **Alzheimer** COVID-19: 0.04% Control: 0.0% P<.001	COVID-19: 2.1% Control: 0.7% P<.001 for both outcomes			P<.001

Author, year Country Sample Size (COVID-19/ control) Description of Controls	ICU Admission (%) Assessment Time Post-Discharge	Pulmonary Outcomes	Cardio-vascular Outcomes	Neurologic and Cognitive Outcomes	Renal Outcomes	Endocrine Outcomes	Gastro-intestinal Outcomes	Hematologic Outcomes
		Risk difference 1.5% (95%CI 1.14, 1.98) P<.001 for all outcomes						
Nugent, 2021(5) USA 182/1430 Concurrent controls; hospitalized, with AKI, negative test for COVID-19; analysis adjusted for demographic, comorbidity, and kidney function factors	37% COVID-19=93 days Controls=61 days	**NR**	**NR**	**NR**	**Kidney Recovery after Discharge** (rate per 100 patient-days) COVID-19 Group (n=32) 0.95 (0.62, 1.46) Non-COVID Group (n=287) 1.74 (1.51, 2.00) HR (adj): 0.57 (0.35, 0.92); P=.02	**NR**	**NR**	**NR**
Puntmann, 2020(6) Germany 100[b]/50 healthy controls/57 risk-factor matched controls	NR COVID-19/ Controls=NR (median time from diagnosis to	**NR**	**CMR LGE** Myocardial COVID-19: 32% Control: 0% Risk Factor-matched Control: 17%	**NR**	**NR**	**NR**	**NR**	**NR**

Author, year Country Sample Size (COVID-19/ control) Description of Controls	ICU Admission (%) Assessment Time Post-Discharge	Pulmonary Outcomes	Cardio-vascular Outcomes	Neurologic and Cognitive Outcomes	Renal Outcomes	Endocrine Outcomes	Gastro-intestinal Outcomes	Hematologic Outcomes
[b]only 33% of COVID-19 group was hospitalized Healthy controls: normotensive, taking no cardiac medications, normal cardiac volume and function Risk-factor matched: pre-COVID patients, matched on demographic and comorbidity factors including known coronary artery disease	CMR was 71 days)		P<.05 **Pericardial** COVID-19: 22% Control: 0% Risk Factor-matched Controls: 14% **Pericardial Effusion >10 mm** COVID-19: 20% Control: 0% Risk Factor-matched Control: 7% P<.05 **Detectable hsTNT ≥3 pg/mL** COVID-19: 71% Control: 22% Risk Factor-matched Control: 54% P<.05 **Significantly elevated hsTNT ≥13.9 pg/mL**					

Author, year Country Sample Size (COVID-19/ control) Description of Controls	ICU Admission (%) Assessment Time Post-Discharge	Pulmonary Outcomes	Cardio-vascular Outcomes	Neurologic and Cognitive Outcomes	Renal Outcomes	Endocrine Outcomes	Gastro-intestinal Outcomes	Hematologic Outcomes
			COVID-19: 5% Control: 0% Risk Factor-matched Control: 0% P<.05					
Raman, 2021(7) United Kingdom 58/30 Concurrent controls; community dwelling, negative for SARS-CoV-2 and asymptomatic, group matched for demographic and comorbidity factors	36% COVID-19 36 days (median) Controls not applicable	**FVC <80% Predicted** COVID-19: 13% Control: 0% P=.09 **FEV_1<80% Predicted** COVID-19: 10.7% Control: 0.4% P=.42 **Dyspnea – mMRC ≥2** (significant breathlessness) COVID-19: 64.3% Control: 10.3% P<.0001 **Lung Parenchymal Abnormalities** COVID-19: 60.4% Control: 10.7%	**Left Ventricular Function** Normal and comparable between groups (data NR) **LGE Myocarditis** COVID-19: 12% Controls: 7% P=.47 **Pericardial Effusion >10 mm** COVID-19: 2% Controls: 0% P=1.0 **Abnormal Troponin T** COVID-19 0% Controls 0%	**MoCA <26** (Abnormal) COVID-19: 28% Control: 17% P=.30 (calculated)	**Residual Renal Impairment, new onset** COVID-19: 3%	**NR**	**NR**	**NR**

Author, year Country Sample Size (COVID-19/ control) Description of Controls	**ICU Admission (%) Assessment Time Post-Discharge**	**Pulmonary Outcomes**	**Cardio-vascular Outcomes**	**Neurologic and Cognitive Outcomes**	**Renal Outcomes**	**Endocrine Outcomes**	**Gastro-intestinal Outcomes**	**Hematologic Outcomes**
		P<.0001 **VO_2 Peak <80% of Predicted Maximum** COVID-19: 54.9% Control: 7.4% P<.0001						
Roberts, 2020(8) United Kingdom 1,877/18,159 Historical controls; discharged from hospital following medical admission (pre-COVID)	11% critical care COVID-19/ Controls=8 days (median)	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**VTE** COVID-19: 0.5% 2 DVT, 7 PE Control (Medical Admissions in 2019): 0.3% 8 proximal, 10 distal, 5 line-associated upper-limb DVT, 33 PE OR 1.60 (95%CI 0.77, 3.10) P=.2
Xiong, 2021(9) China 538/184 Concurrent controls; non hospitalized,	NR COVID-19/ Controls=97 days (median)	**NR**	**Newly Diagnosed Hypertension** COVID-19: 1% Control: 0%	**NR**	**NR**	**NR**	**NR**	**NR**

Author, year Country Sample Size (COVID-19/ control) Description of Controls	ICU Admission (%) Assessment Time Post-Discharge	Pulmonary Outcomes	Cardio-vascular Outcomes	Neurologic and Cognitive Outcomes	Renal Outcomes	Endocrine Outcomes	Gastro-intestinal Outcomes	Hematologic Outcomes
non-COVID with similar demographics								

[a]Includes participants without history of the outcome in the past one year

Abbreviations: AKI=acute kidney injury; CI=confidence interval; CKD=chronic kidney disease; CMR=cardiovascular magnetic resonance; COVID-19=SARS-CoV-2: 2019 novel coronavirus; DVT=deep venous thrombosis; FEV1 =forced expiratory volume in 1 sec; FVC=forced vital capacity; HR=hazard ratio; hsTNT=high-sensitivity Troponin T; LGE=late gadolinium enhancement; LVEF=left ventricular ejection fraction; mMRC=modified Medical Research Council; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; NR=not reported; OR=odds ratio; PE=pulmonary embolism; VTE=venous thromboembolism

Supplemental Table 4. Quality Ratings for Studies with Control Groups (shaded columns are database studies)

Criteria*	Al-Aly 2021(1)	Ayoubkhani 2021(2)	Chevinsky 2021(3)	Daugherty 2021(4)	Nugent 2021(5)	Puntmann 2020(6)	Raman 2021(7)	Roberts 2020(8)	Xiong 2021(9)
Were groups similar/recruited from same population?	No	No	Yes	No	Yes	Unclear	No	No	No
Was exposure measured similarly?	N/A	N/A	Yes	Yes	Yes	N/A	Yes	N/A	Unclear
Was exposure measured in valid and reliable way?	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Were confounding factors identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Were participants free of outcome at moment of exposure?	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes
Were outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear

Criteria*	Al-Aly 2021(1)	Ayoubkhani 2021(2)	Chevinsky 2021(3)	Daugherty 2021(4)	Nugent 2021(5)	Puntmann 2020(6)	Raman 2021(7)	Roberts 2020(8)	Xiong 2021(9)
Was follow-up time reported and sufficient† for outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes
Was follow-up complete? If not, were reasons for loss described and explored?	Yes	Yes	Unclear	Yes	No/Yes – described	Yes	Yes	No/No	No/Yes - described
Were strategies to address incomplete follow-up utilized?	N/A	N/A	Unclear	N/A	Yes	N/A	No	No	No
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

N/A=not applicable

*JBI Critical Appraisal Checklist for Cohort Studies. Source: Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. In Aromataris E, Munn Z (Eds) JBI Manual for Evidence Synthesis. JBI, 2020. Available from https://sysnthesismanual.bji.global. Accessed October 8, 2021.

†For this manuscript, ≥90 days was considered sufficient

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