COVID-19 Post-acute Care Major Organ Damage: A Living Rapid Review

Updated September 2021

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Prepared by:
Evidence Synthesis Program (ESP) Center
Minneapolis VA Health Care System
Minneapolis, MN
Timothy J. Wilt, MD, MPH, Director
Wei Duan-Porter, MD, PhD, Associate Director

Authors:
Nancy Greer, PhD
Bradley Bart, MD
Charles Billington, MD
Susan J. Diem, MD, MPH
Kristine E. Ensrud, MD, MPH
Anjum Kaka, MD
Mark Klein, MD
Anne Melzer, MD, MS
Scott Reule, MD
Aasma Shaukat, MD, MPH
Kerry Sheets, MD
Jamie Starks, MD
Orly Vardeny, PharmD, MS
Lauren McKenzie, MPH
Benjamin Stroebel, MPH
Roderick MacDonald, MS
Katie Sowerby, BA
Wei Duan-Porter, MD, PhD
Timothy J. Wilt, MD, MPH

WHAT'S NEW

Updated September 2021
Search current as of May 19, 2021

Prevalence estimates have been updated to include 34 new studies (124 total). Recent evidence includes 4 large database studies with control groups. Evidence from these studies suggests increased risk for disease in adults hospitalized for COVID-19. Limitations of the available evidence include poorly described study populations, lack of patient-centered clinical outcomes, and few control groups or pre-COVID-19 data. Outcomes following COVID variants are unknown.

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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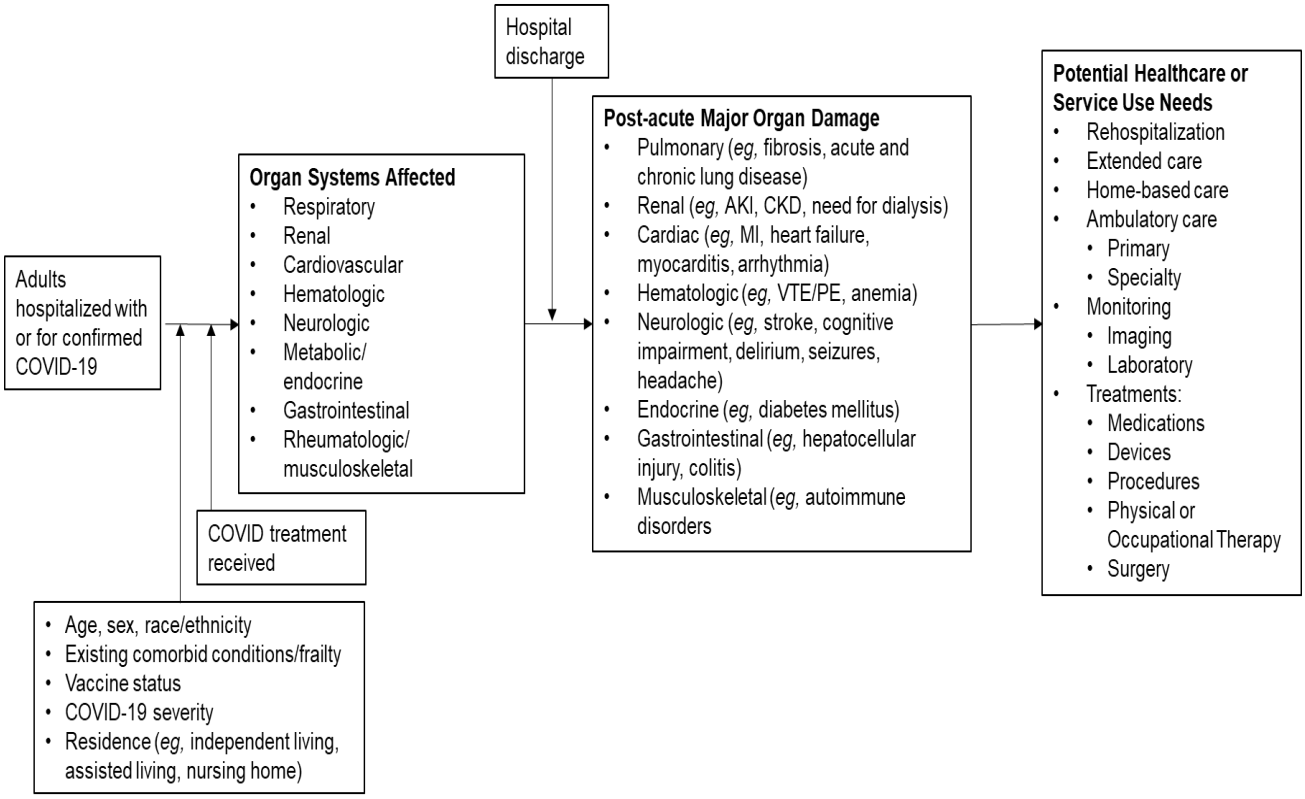
BACKGROUND

Coronavirus disease-2019 (COVID-19) is a viral illness that, as of August 30, 2021, was identified in over 216 million individuals (over 38 million in the US) in over 220 countries, areas, or territories (https://www.who.int/emergencies/diseases/novel-coronavirus-2019, https://coronavirus.jhu.edu/, https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days). Over 4.5 million deaths worldwide (over 637,000 in the US) are attributed to COVID-19. Within the VA, as of August 30, 2021, 13,601 deaths and 284,532 convalescent cases have been reported based on publicly available data (https://www.accesstocare.va.gov/Healthcare/COVID19NationalSummary), though these figures likely underestimate the number of Veterans receiving VA healthcare infected with and dying from COVID-19. COVID-19 is caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and was declared a pandemic by the World Health Organization on March 11, 2020. In addition to the potential for severe pulmonary disease, there have been numerous reports of other major organ system manifestations and complications in patients hospitalized with COVID-19 including cardiovascular,[1,2,3] renal,[4,3,5] neurological,[6,7] hematologic,[3,8-10] endocrine,[3,11] and gastrointestinal.[3,12]

Persistent *symptoms* have been reported in patients following recovery from acute COVID-19, with fatigue, shortness of breath, muscle or body pain, and difficulty concentrating being most common.[13-17] Multi-organ damage[18] and long-term clinical outcomes[19] following other coronavirus outbreaks – severe acute respiratory syndrome (SARS) and Middle East Respiratory syndrome (MERS) – have been reported, suggesting the potential for similar multi-organ damage and adverse long-term clinical outcomes with COVID-19 infections. In addition, because many COVID-19 patients are admitted to intensive care units, outcomes similar to those observed in post-intensive care syndrome or post-sepsis syndrome have also been suggested as possible long-term consequences of COVID-19 infections.[20]

The purpose of this living rapid review is to determine the prevalence of post-acute care major organ damage and healthcare or service use needs associated with major organ damage in adults who were hospitalized with or for COVID-19. Our review is limited to post-hospital major organ damage or healthcare/service use needs – a subset of post-acute sequelae of SARS-CoV-2 infection (PASC) as described by the National Institutes of Health (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study). The topic was nominated by the VA Evidence Synthesis Program Coordinating Center in collaboration with VHA clinical and operations partners in order to guide future clinical care decisions and resource needs related to COVID-19. It is 1 in a series of 3 living rapid reviews conducted across VA ESP sites addressing post-acute care prevalence related to: 1) mental health, 2) rehabilitation/ functional status, and 3) major organ damage in patients hospitalized with or for COVID-19. Our analytic framework is shown in Figure 1.

Figure 1. Analytic Framework



KEY QUESTIONS AND SCOPE

Key Question 1: What is the post-acute care prevalence of major organ damage among adults hospitalized with or for proven COVID-19 disease?

Key Question 2: Does the post-acute care prevalence of major organ damage among adults with or for COVID-19 disease vary by patient characteristics (*eg,* age, sex, race/ethnicity, preexisting co-morbidities/frailty, place of residence), COVID-19 disease severity, or other factors (*eg*, treatment for COVID-19)?

Key Question 3: What are the short- (< 3 months) and long-term (≥ 3 months) healthcare or service use needs of adults surviving COVID-19 disease with major organ damage?

ORIGINAL SCOPE

For the initial report (December 2020) and first update (June 2021), based on consultation with VA Central Office operational partners, we included studies of adults hospitalized for COVID-19 and studies of adults hospitalized for another indication who have a positive COVID-19 test. Additionally, in collaboration with our local clinical content experts we prioritized conditions likely of greatest clinical relevance and included criteria for determining definitions and measures of symptomatic versus asymptomatic as well as acute versus chronic major organ damage. All patients had laboratory-confirmed COVID-19. We defined post-acute to include major organ damage or healthcare/service use needs reported on the day of hospital discharge or

any time post-discharge. We included studies reporting "surrogate measures" (*eg*, a radiologic or laboratory measure consistent with a definition of a disease such as pulmonary function tests, radiographic pulmonary abnormalities, laboratory liver function tests or imaging studies, creatinine, glucose or hemoglobin A1c values, cardiac imaging defined as abnormal, or imaging studies for venous thromboembolism). We excluded studies reporting only mean or median values for these tests, as mean or median values do not provide a reliable measure of organ damage prevalence or healthcare/service use. We also excluded studies reporting only general symptoms (*eg*, fatigue, pain), and did not extract these data from included studies, because symptoms are not specific to a disease or organ damage. We included studies reporting on dyspnea as we determined dyspnea to be most consistent with pulmonary or cardiac damage. As noted above, post-acute mental health and functional status are addressed in separate ESP reviews. We excluded studies of children and studies of adults who had COVID-19 but were not hospitalized. We also excluded studies that did not provide information at the time of or after hospital discharge even if they included patient information during hospitalization.

UPDATED SCOPE – SEPTEMBER 2021 UPDATE

For the September 2021 (final) update of the review, we made minor changes to the scope. These changes reflect the growing body of literature on post-acute COVID-19. For the September 2021 update:

1. we only report outcomes post-discharge (*ie,* studies only reporting outcomes at the time of discharge were excluded),

2. we required a minimum of 50 patients with COVID-19, and

3. we only reported healthcare/resource utilization outcomes that were specific to major organ damage (*ie,* all-cause readmission was no longer an outcome of interest).

METHODS

Our protocol was registered in PROSPERO: CRD42020204788.

SEARCH STRATEGY

We searched MEDLINE, Embase, and the Cochrane Library. Our initial report (December 2020) included studies identified in a search from January 1, 2019 to October 6, 2020. The first update (June 2021) included studies identified in a search through January 12, 2021. This version of the report (September 2021) includes studies identified in a search through May 19, 2021. The search strategy (Appendix A) was developed with input from expert medical librarians. We also reviewed non-peer-reviewed public postings about post-COVID-19 complications for links to peer-reviewed data reports.

SCREENING PROCESS

Consistent with established rapid review methods, abstracts were reviewed by 1 investigator. A subset of 200 abstracts underwent dual independent review with substantial agreement between the 2 investigators. All articles identified as potentially eligible based on abstract review were

independently reviewed by 2 investigators at the full-text level. Reasons for exclusion were noted. Conflicts were resolved by discussion. Our inclusion and exclusion criteria are reported in Table 1. We did not require studies to include a comparison group nor did we require that studies provide information about "pre-COVID-19" health status/conditions or the primary reason for hospitalization (*ie, due to* COVID-19 compared to *for other conditions* where COVID-19 may be a contributing factor or identified incidentally on screening).

Table 1. Study Eligibility Criteria

Study Characteristic	Include	Exclude
Population	Adults (age 18 and older)	Children or adolescents, age <18; MERS; SARS
Intervention	Discharge from hospitalization after admission with or for proven COVID-19[a]	Data only collected from patients during ongoing hospital acute-care admission with or for proven COVID-19
Comparator	Discharge from hospitalization for individuals without COVID-19 (ideally another respiratory condition); a comparator was not required	Not applicable
Outcomes	Prevalence and severity of major organ damage (respiratory, renal, cardiovascular, hematologic, neurologic, metabolic/ endocrine, gastrointestinal, and rheumatologic/musculoskeletal); healthcare or service use needs related to major organ damage[b]	No outcomes of interest
Timing	Short-term (< 3 months) and long-term (≥ 3 months) post-discharge	Not applicable
Setting	Any post-discharge setting (*eg*, home, rehabilitation or long-term care facility); may include re-hospitalization	Not applicable
Study Designs	Cohort, case series, other observational; may prioritize articles using a best-evidence approach	Case report, narrative review, descriptive/opinion article with no data

[a]In the original and first update, we reported outcomes at the time of discharge. For the September 2021 update, patients must be discharged with post-discharge outcome data available.
[b]In the original report, we included studies reporting "re-positive" RT-PCR test results following discharge. For the June 2021 update, we excluded studies only reporting "re-positive" 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 recognized that patients may be PCR positive for prolonged periods after an initial COVID 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.

DATA ABSTRACTION

Study characteristics (location, design, funding), study inclusion and exclusion criteria, baseline demographic data (age, sex, race, comorbidities), hospitalization characteristics (COVID-19 severity, ICU admission, mechanical ventilation, length of hospital stay), length of time post-hospital, and outcomes data were abstracted by 1 investigator and verified by a second. Discrepancies were resolved by discussion.

RISK OF BIAS ASSESSMENT

We did not formally rate risk of bias of individual studies.[21] We assessed study quality characteristics using the Joanna Briggs Critical Appraisal Tool for case series[22] taking into account clarity of inclusion criteria and completeness of inclusion, use of standard methods for identification and assessment of the condition, and inclusion of adequate information about the subjects and setting.

SYNTHESIS

Due to heterogeneity in study populations, study designs, and methods of outcome assessment, we were unable to pool most outcomes data. We used R (http://www.rstudio.com/) to calculate random effects pooled estimates for 3 pulmonary outcomes. We narratively synthesized the remaining evidence.

LIVING REVIEW

Our review was updated approximately every 3 months through September 2021, using the literature search strategy outlined above to identify evidence related to post-acute major organ damage and associated healthcare/service use needs. Study eligibility criteria were modified based on increased reporting of post-acute outcomes in published studies. Procedures for data abstraction and risk of bias assessment remained the same. Our data synthesis plan was reviewed at the time of each update but remained unchanged.

PEER REVIEW

A draft version of each update of this report will undergo peer review by content experts and clinical leadership. Reviewer comments and our responses will be presented in Appendix B and the final report will incorporate the comments.

RESULTS

KEY FINDINGS

Key Question 1: Recent evidence includes 4 large database studies, 2 from the US including 1 study of US Veterans, identifying post-hospitalization, incident respiratory, cardiac, neuromuscular, endocrine, renal, gastrointestinal, and hematologic disease in COVID-19 and control groups. However, the majority of studies enroll convenience samples without controls, providing wide-ranging prevalence estimates based mainly on physiologic data.

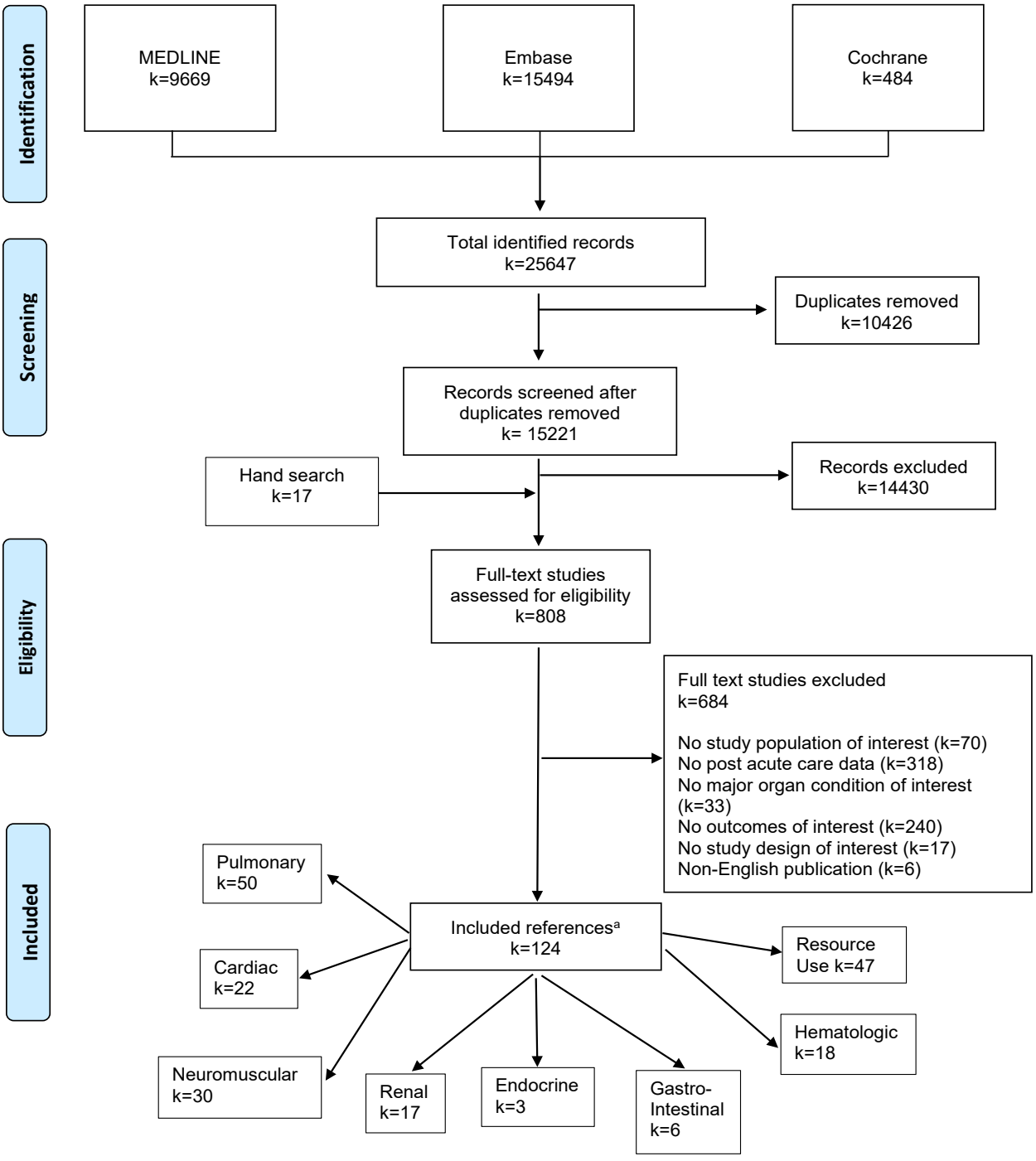
Key Question 2: Information is insufficient to assess if prevalence varies by patient, disease, and comorbidity factors.

Key Question 3: Post-hospitalization resource use including discharge disposition and readmission varies by outcome definition and timing. Results are limited by use of convenience samples and lack of controls.

PRISMA FLOW DIAGRAM

The results of our literature search and study selection process are depicted in Figure 2.

Figure 2. PRISMA Flow Diagram



[a]Studies may have reported more than 1 category of outcomes

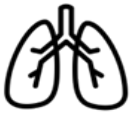
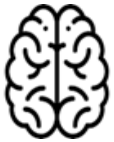
OVERVIEW OF INCLUDED STUDIES

Our December 2020 report included 42 studies. After removing 3 of those studies only reporting "re-positive" results (see Table 1 footnote b) and adding 51 studies identified in the literature search through January 2021, we included 90 studies in the June 2021 update. For the current version of the report, with a literature search through May 19, 2021 and with modified inclusion criteria as noted above, we added 34 new studies. Outcomes data (Table 2) were reported at the time of hospital discharge (k=35, none of which were from the May 2021 search per modified inclusion criteria),[23-55] post-discharge (31 studies at 30 days or fewer follow-up and 17 at 3 months or longer) (k=81),[56-135] or both (k=7, again, none from the May 2021 search).[136-142] One study did not report time post-hospitalization.[143]

Fifty studies reported pulmonary outcomes,[24,27,29,30,34,45,55,57,60,61,63,71,73-75,81,82,85,88,91,94-96,100,101,103,104,106-110,115-120,122,124,126-128,130,132-134,141,143,144] 22 studies reported cardiovascular outcomes,[24,57,62,66,75,81,82,96,99,104,106,110-112,114,115,120,123,124,127,131,135] 30 reported neuromuscular outcomes,[23,25,31,33,36,39,46,48,53,61,77,81,82,91,104,105,109-111,114,117,120,122,124,125,127,129,130,132,142] 17 reported renal outcomes,[35,47,49,57,83,85,97,102,104,106,109,110,120,121,124,139,140,145] 3 reported endocrine outcomes,[104,106,110] 6 reported gastrointestinal outcomes,[57,85,104,106,110,111] 18 reported hematologic outcomes,[24,65,68,75,79,81,84,85,92,93,98,104,109,110,113-115,126] and 47 reported healthcare or resource utilization outcomes.[26,28,31,32,37,38,40-44,47,50-52,54,56,58,59,64,65,67,69-72,76-78,80-83,85-87,89,90,112,127,128,136-138,142,143,146] Studies were typically described as retrospective, case series, or cross-sectional, although 38 reported that data were collected prospectively [23,24,38,49,57,58,61,66,68,71,75,78,81,82,86,94-96,99,103,105,107,108,111,113,116-120,123-125,131,132,135,142,147] including 18 of the 34 studies added for the September 2021 version of the review. Study inclusion and exclusion criteria, patient demographics, and hospitalization characteristics are reported in Appendix C, Table 1.

Study quality assessments are reported in Appendix C, Table 2. In 36% (45/124) of the studies, it was unclear whether all patients were assessed for eligibility or whether consecutive patients were enrolled. Fifty-six percent (69/124) were conducted at a single site. In 39% (48/124), fewer than 100 patients were enrolled (for the September 2021 update with fewer than 50 COVID-19 cases were excluded). Training and experience of individuals abstracting data from medical records, administering tests, or interpreting imaging results was rarely reported. Although many studies obtained data from electronic medical records, it was often unclear what data were abstracted (*eg,* ICD codes). Many studies did not report COVID-19 severity; among those that did, different criteria were used. Pre-existing comorbidities and COVID-19 severity were rarely linked to outcomes.

Table 2. Overview of Included Studies

								
	Pulmonary	**Cardiac**	**Neuro-muscular**	**Renal**	**Endocrine**	**Gastro-intestinal**	**Hematologic**	**Resource Use**
Number of Studies Reporting[a]	50	22	30	17	3	6	18	47
Outcomes Frequently Reported (number of studies reporting the outcome)	Respiratory Disease (5) Fibrosis (12) CT Abnormalities (15) Impaired Pulmonary Function (20) Dyspnea (26)	Cardio-vascular Disease (9) Impaired or Reduced EF (8) Fibrosis and/or Inflammation (by cMRI) (3) Pericardial Effusion (6) Elevated hsTNT (3)	Stroke (6) Neuro-cognitive Disorders (4) Cognitive Impairment (9) Cognitive symptoms (11) Modified Rankin Scale Scores (8) Neuro-muscular (2)	CKD (3) AKD (at- and post-discharge) (5) Persistent Kidney Dysfunction (3) Need for RRT (8)	Diabetes (3)	Gastro-intestinal Disease (2) Liver Test Abnormalities (2) Liver Imaging Abnormal-ities (2)	Thrombo-embolism (18) Bleeding Events (3) Coagulation Disorders (3)	Discharge Disposition (24) Readmission (22) Oxygen Therapy (9) Post-Acute Care (8)

Abbreviations: AKD=acute kidney disease; cMRI=cardiovascular magnetic resonance imaging; EF=ejection fraction; hsTNT=high-sensitivity Troponin T; RRT=renal replacement therapy

[a]Studies may have reported more than 1 category of outcomes

PULMONARY OUTCOMES

Key Findings

Interpretation of findings is limited by varying degrees of COVID-19 severity and different outcome definitions, assessment methods, sampling strategies, and follow-up lengths across studies.

In studies with control groups, incident respiratory disease may be higher in post-hospitalization COVID-19 cases (k=3). Prevalences ranged from 2% to 22% in COVID-19 groups compared to less than 1% in control groups. Dyspnea was more prevalent (64% vs 10%) or Veterans were at greater risk for dyspnea (HR 1.14 [95%CI 1.04, 1.26]) in COVID-19 groups than in control groups. Other reported pulmonary outcomes included radiographically defined fibrosis at varying time intervals (k=12, none with control groups) with estimates ranging from 0% to 61% of enrolled patients, abnormal diffusing capacity of the lung for carbon monoxide (DLCO) in 16% to 57% (k=15, none with control groups), and dyspnea present at greater than 1 month post-discharge in 2 to 81% (k=26, including 2 with control groups noted above).

Overview of Studies

Of the 50 studies reporting pulmonary outcomes (Appendix C, Tables 1 and 3), 18 were from Europe,[27,29,30,60,61,81,82,96,107,108,118,120,126-128,130,132,144] 16 were from China,[34,45,55,63,71,73,74,85,88,100,101,103,116,119,133,141] 5 were from the US,[91,104,109,110,117] 5 were from the UK,[57,106,115,124,143] 3 were from the Middle East,[24,75,94] 2 were from Africa,[122,134] and 1 was from Canada.[95] Sample sizes ranged from 18 to 29,335 COVID-19 patients, with only 5 studies enrolling over 1000 individuals and 18 studies enrolling fewer than 100 individuals. Mean or median ages ranged from 37 to 73 years and the percentage of males enrolled ranged from 38% to 94%. Only 7 studies reported race with 14% to 78% White and 5% to 34% Black. A history of chronic obstructive pulmonary disease (COPD) was reported in 0% to 19% of participants (29 studies) and a history of smoking in 0% to 44% (22 studies). Thirteen studies reported the percentage of study participants with severe or critical COVID-19. Four studies enrolled only patients with severe COVID-19.[24,75,116,133] Of the remaining 16 studies, fewer than 50% were classified as severe in 13 studies. Three studies excluded patients who received mechanical ventilation.[34,81,147] Five of the studies (4 of which were large database studies) included a comparison to non-COVID-19 patients.[104,106,109,110,124] Reported outcomes varied across the studies, with most reporting surrogate measures of health outcomes.

Respiratory Disease

Studies with Control Groups

Three large database studies reported incident respiratory disease. A study from the UK, with over 56,000 records, reported a statistically significant difference (P<.001) in new onset respiratory disease between the COVID-19 (22% [6,085/28,335]) and general population control (0.8% [240/28,335]) groups at approximately 146 days post-discharge.[106] A study from the US, with over 54,000 records, reported odds ratios for new onset pneumonia (except that caused by tuberculosis) in the COVID-19 group versus a hospitalized non-COVID control group.[109] At 1-30 days post-discharge, the odds ratio was statistically significant (OR 5.5 [95%CI 4.1, 7.5]); at 31-60, 61-90, and 91-120 days post-discharge, the odds ratio was no longer statistically

significant. A similar pattern was observed for "respiratory failure, insufficiency, or arrest" with an odds ratio of 3.3 (95%CI 2.6, 4.1) at 0-30 days post discharge and non-statistically significant odds ratios at the other follow-up times. A study from the US, with over 36,000 records, reported a higher incidence of overall respiratory failure in the COVID-19 group (2.6%) than in a non-COVID control group (0.2%) (P<.001) at 4 months after acute illness.[110] The pattern was the same when acute respiratory failure, chronic respiratory failure, and interstitial lung disease were evaluated separately.

Studies without Control Groups

Two smaller studies without control groups also reported respiratory disease. A study from Italy reported no incidence of respiratory failure at 60 days post-discharge.[127] Fifty-nine percent of the study participants had severe or critical COVID-19. A study from France reported emphysema in 18% (10/55) patients at a median of 144 days post-discharge.[126] Participants in this study were experiencing residual symptoms during a clinic evaluation at 3 months. After referral to the pulmonology department, those with residual symptoms not explained by pre-existing respiratory disease underwent CT evaluation.

Radiographic Fibrosis

Twelve studies, none with control groups, reported the percentage of patients with pulmonary fibrosis (Table 3). Definitions of fibrosis varied across studies with broad to very specific criteria; 4 studies did not provide a definition. In some studies, evaluation for fibrosis was limited to those most ill with lingering symptoms.

Table 3. Radiographic Pulmonary Fibrosis (shaded rows indicate studies added for September 2021 update)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Definition/ Assessment	Pulmonary Fibrosis
Hu, 2020[45] China	17% severe	Discharge	Artificial intelligence to calculate fibrosis volume or % of fibrosis in entire lung	61% (46/76)
Yu, 2020[74] China	ICU admission: 16%	9 days post-discharge (median)	Fibrosis: combination of parenchymal bands, irregular interfaces, course reticular pattern, and traction bronchiectasis	44% (14/32)
Zhang, 2020[100] China	17% severe	14 days post-discharge	NR	31% (35/112)
Hall, 2021[115] United Kingdom	ICU admission: 39%	28-42 days post-discharge	Poorly defined; "persistent interstitial change" per interpreting radiologist	32% (64/200)
Huang Y, 2020[63] China	30% severe	30 days post-discharge	NR	7% (4/57)
You, 2020[73] China	34% severe/critical	40 days post-discharge (mean)	NR	22% (4/18)

Yasin, 2021[134] Egypt	ICU admission: 25%	42 days post-discharge (mean)	Parenchymal bands, irregular interfaces (bronchovascular, pleural, or mediastinal), coarse reticular pattern, and traction bronchiectasis	48% (101/210)
Wu, 2021[133] China	100% severe (inclusion criteria)	98 days 189 days 275 days 348 days post-discharge (medians)	'Established fibrosis' (NOTE: study reports abnormalities which may have been included as fibrotic changes as defined by other studies)	0% (0/83)
Boari, 2021[108] Italy	NR	120 days post-discharge	Poorly defined; chest CT confirmed presence of indices of pulmonary fibrosis	25% (24/94)
Morin, 2021[120] France	ICU admission: 30%	125 days post-discharge (median)	NR	19% (33/170) Intubated: 36.7% (18/49) Non-intubated: 12.4% (15/121)
Remy-Jardin, 2021[126] France	ICU admission: 42%	144 days post-discharge (median)	Bronchial/bronchiolar dilatation within areas of ground-glass attenuation	12.7% (7/55)
Han, 2021[116] China	100% severe	175 days post-disease onset (mean)	Features of fibrosis (*ie*, honeycomb cysts) or features potentially suggestive of fibrosis (*ie*, bronchial and/or bronchiolar dilatation within areas of ground-glass opacities and/or reticulation)	Fibrotic-like changes at 6 months: 35% (40/114) de Novo abnormalities: 95% (38/40)

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity

Other Computed Tomography Findings

Several studies reported other findings from computed tomography (CT) (Table 4). Only 1 included a control group.[104]

Table 4. Chest CT Findings (shaded rows indicate studies added for September 2021 update; Author, Year in bold indicates study with comparator group)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Findings
Xia, 2020[55] China	Mild or moderate	Discharge	Residual infiltrates without fibrosis: 82% (233/282) Residual infiltrates and consolidation fibrosis: 14% (39/282)

Liu, 2020[141] China	Mild or moderate	Discharge 14 days 28 days post-discharge (median)	Consolidations D/C: 49% (25/51) 14 d: 8% (4/51) 28 d: 2% (1/51)
Wang, 2020[71] China	53% severe	7-14 days 21-28 days post-discharge	Chest CT Deterioration[c] 7-14 d: 6% (2/36) 21-28d: 0% (0/54)
Zhang, 2020[100] China	83% non-severe	14 days post-discharge	Normal CT 40% (45/112)
Huang Y, 2020[63] China	30% severe	30 days	Residual Abnormality 54% (31/57) Severe: 94% (16/17) Non-severe: 38% (15/40)
Sonnweber, 2020[96] Austria	ICU admission: 22%	63 days 103 days post-diagnosis (means)	Pathological CT 63 d: 77% (112/145 103 d: 63% (84/133)
Shah, 2020[95] Canada	22% requiring mechanical ventilation	90 days post-symptom onset	Abnormal 88% (53/60)
Qin, 2021[103] China	49% severe	90 days post-discharge	Pulmonary Interstitial damage (from subset of 45 patients who received chest CT): 71% (32/45)
Li, 2021[119] China	45% critical/severe	90-180 days post-discharge	Lesions (incomplete resolution) 72% (44/61)
Wu, 2021[133] China	100% severe (inclusion criteria)	98 days 189 days 275 days 348 days post-discharge (medians)	Residual Changes 98d: 78% (65/83) 189d: 48% (40/83) 275d: 27% (22/83) 348d: 24% (20/83)
Morin, 2021[120] France	ICU admission: 30%	125 days post-discharge (median)	Abnormal CT 53% (106/171) Persistent GGO 42% (72/170)
Remy-Jardin, 2021[126] France	ICU admission: 42%	144 days post-discharge (median)	Lung Infiltrates (“residual findings”) 73% (40/55)
Al-Aly, 2021[104] USA (Veterans)	ICU admission: 26%	150 days post-discharge (median)	**Interstitial lung disease (ICD-10)** COVID group: 1.60% Non-COVID Control group: 0.13% Risk difference 1.47% (95%CI 1.14, 1.98)
Huang C, 2021[85] China	ICU admission: 4%	153 days post-discharge (median)	At least 1 Abnormal CT Pattern[b] Scale 3: 52% (49/89) Scale 4: 54% (87/161) Scale 5-6: 54% (50/92)
Han, 2021[116] China	100% severe	175 days post-disease onset (mean)	Pleural Effusions 9% (10/114)

Abbreviations: CT=computed tomography; GGO=ground glass opacity

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]Scale 3=no supplemental oxygen; Scale 4=requiring supplemental oxygen; Scale 5-6=requiring high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation
[c]Outcomes did not differ by COVID-19 severity

Other Imaging

Studies with Control Groups

An MRI study reported lung parenchymal abnormalities in 60% (32/53) of the COVID-19 group and 11% (3/28) of the non-COVID control group at a median of 144 days post-discharge.[124]

Studies without Control Groups

One study reported "lung abnormalities" (worsening or appearance of X-ray pulmonary infiltrates) in 85% (6/7) at the time of hospital discharge.[30] Patients in this study were all receiving maintenance hemodialysis at the time of hospitalization.

Another study measured lung impairment with MRI at a median of 105 days after a positive COVID-19 result.[57] Deep breathing fractional area change of <31% was observed in 12% (4/34) evaluated.

Pleural effusions were detected using point-of-care ultrasound in 2% (1/64).[24] At ICU admission, pleural effusions had been observed in 22.4% (20/89). A second study reported pleural effusions in 19% (24/127) at 2 months and 12% (15/127) at 4 months post-discharge.[75] Both studies enrolled patients admitted to the ICU, most of whom required invasive mechanical ventilation.

Pulmonary Function

Pulmonary function tests were reported by 20 studies (Table 5). Studies reporting abnormal forced expiratory volume in 1 second (FEV_1) are shown in Figure 3, abnormal forced vital capacity (FVC) in Figure 4, and abnormal DLCO in Figure 5. Abnormal was defined as either <80% predicted or described by the author as abnormal (see Table 5). At follow-up periods of up to 348 days, FEV_1 was reported to be abnormal in 9% to 25%, FVC was reported to be abnormal in 4% to 27% and DLCO was reported to be abnormal in 16% to 57%.

Studies with Control Groups

Only 1 study included a control group and found no statistically significant difference between COVID-19 cases and non-hospitalized, non-COVID cases for either FEV_1 or FVC at a median of 48 days post-discharge.[124]

Table 5. Pulmonary Function Test Findings (shaded rows indicate studies added for September 2021 update; Author, Year in bold indicates study with comparator group)

Author, Year Country	Time of Assessment (post-discharge unless noted)	COVID-19 Severity[a]	FEV_1 <80% Predicted (unless noted)	FVC <80% Predicted (unless noted)	DLCO <80% Predicted (unless noted)
Frija-Masson, 2020[60] France	30 days after symptom onset	50% severe	Abnormal lung function: 52% (26/50)		
Mo, 2020[34] China	Discharge	17% severe	14% (15/110)[b]	9% (10/110)[b]	47% (51/110) Mild: 30% (7/24) Pneumonia: 42% (28/67) Severe: 84% (16/19) P<.01 Severe vs others
Lv, 2020[88] China	14 days post-discharge	20% severe	NR	24% (33/137) Severe: 56% (15/27) Non-severe: 16% (18/110)	NR
Hall, 2021[115] United Kingdom	28-42 days post-discharge	ICU admission: 39%	NR	27% (16/59) with complete lung function tests	NR
Huang Y, 2020[63] China	30 days post-discharge	30% severe	9% (5/57)[c]	11% (6/57)[c]	53% (30/57) Severe: 77% (13/17) Non-severe: 43% (17/40) P=.02
You, 2020[73] China	40 days post-discharge (mean)	34% severe or critical	17% (3/18)[b]	17% (3/18)[b]	NR
Ramani, 2021[91] USA	40 days post-discharge (median)	86% requiring mechanical ventilation	Abnormal lung function: 39% (10/26)		Reduced diffusion capacity: 27% (7/26)
Raman, 2021[124] United Kingdom	48 days post-discharge (median)	ICU admission: 36%	11% (6/56) Controls 4% (1/28) P=.42	13% (7/56) Controls 0% (0/28) P=.09	NR
Sonnweber, 2020[96] Austria	63 and 103 days post-diagnosis (means)	ICU admission: 22%	63 d: 22% (28/127) 103 d: 22% (30/136)	63 d: 27% (34/125) 103 d: 22% (29/132)	63d: 31% (39/125) 103d: 21% (28/133)
Venturelli, 2021[132] Italy	81 days post-discharge (median)	ICU admission: 9%	NR	NR	Reduced: 19% (136/716)

Author, Year Country	Time of Assessment (post-discharge unless noted)	COVID-19 Severity[a]	FEV_1 <80% Predicted (unless noted)	FVC <80% Predicted (unless noted)	DLCO <80% Predicted (unless noted)
Shah, 2020[95] Canada	90 days post-symptom onset	ICU admission: 16%	NR	NR	Abnormal: 52% (31/60)
Zhao, 2020[101] China	90 days post-discharge	7% severe	Abnormal: 11% (6/55)	Abnormal: 11% (6/55)	Abnormal: 16% (9/55)
Qin, 2021[103] China	90 days post-discharge	49% severe	NR	21% (17/81)	54% (44/81)
Sibilia, 2021[144] Spain	101 days post-discharge (mean)	71% severe	25% (43/172)	24% (42/171)	57% (98/172)
Bellan, 2021[107] Italy	90-120 days post-discharge	ICU admission: 12%	NR	NR	52% (113/219)
Wu, 2021[133] China	98, 189, and 348 days post-discharge (medians)	100% severe (inclusion criteria)	98d: 30% (25/83) 189d: 24% (20/83) 348d: 16% (13/83)	98d: 23% (19/83) 189d: 16% (13/83) 348d: 11% (9/83)	98d: 55% (46/83) 189d: 54% (45/83) 348d: 33% (27/83)
Boari, 2021[108] Italy	120 days post-discharge	NR	NR	NR	32% (30/94)
Morin, 2021[120] France	125 days post-discharge (median)	NR	NR	NR	<70% Predicted 22% (33/152)
Huang C, 2021[85] China	153 days post-discharge (median)	ICU admission: 4%	Overall: 6% (22/349) Scale 3: 8% (7/89)[c] Scale 4: 2% (4/172) Scale 5-6: 13% (11/88)	Overall: 4% (14/349) Scale 3: 3% (3/89)[c] Scale 4: 1% (1/172) Scale 5-6: 11% (10/88)	Overall: 34% (114/336) Scale 3: 22% (18/83)[c] Scale 4: 29% (48/165) Scale 5-6: 56% (48/88)
Han, 2021[116]	175 days post-disease onset (mean)	100% severe (inclusion criteria)	NR	NR	26% (27/104)

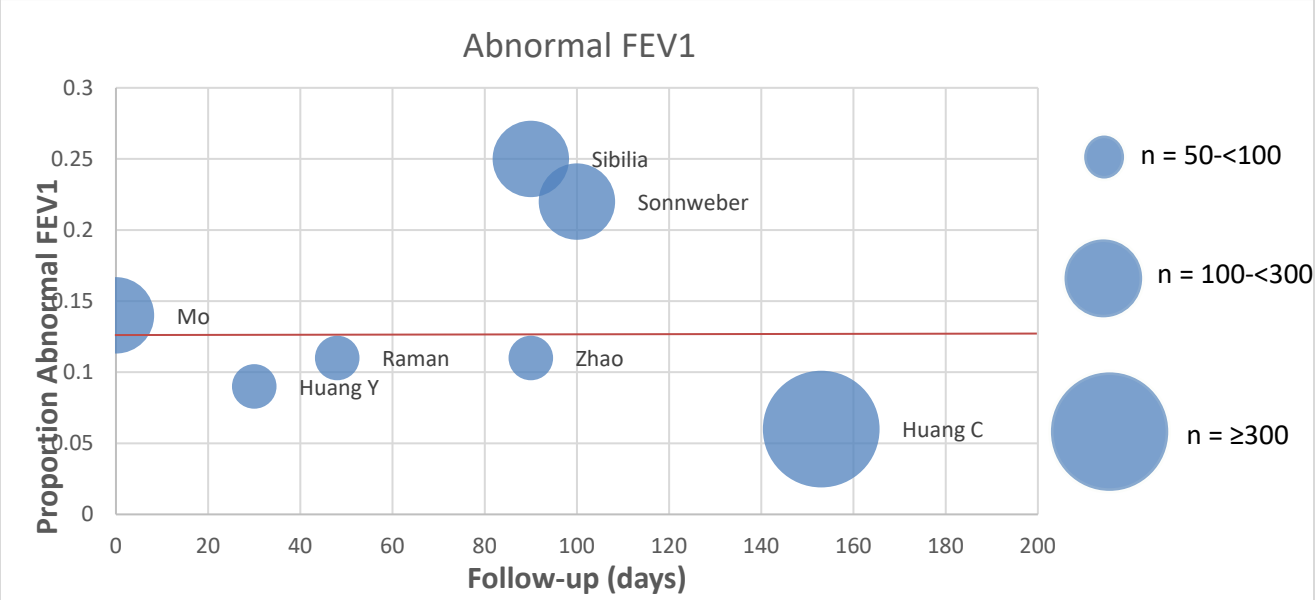
Abbreviations: DLCO=diffusing capacity of the lung for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity

[b]Outcomes did not differ by COVID-19 severity

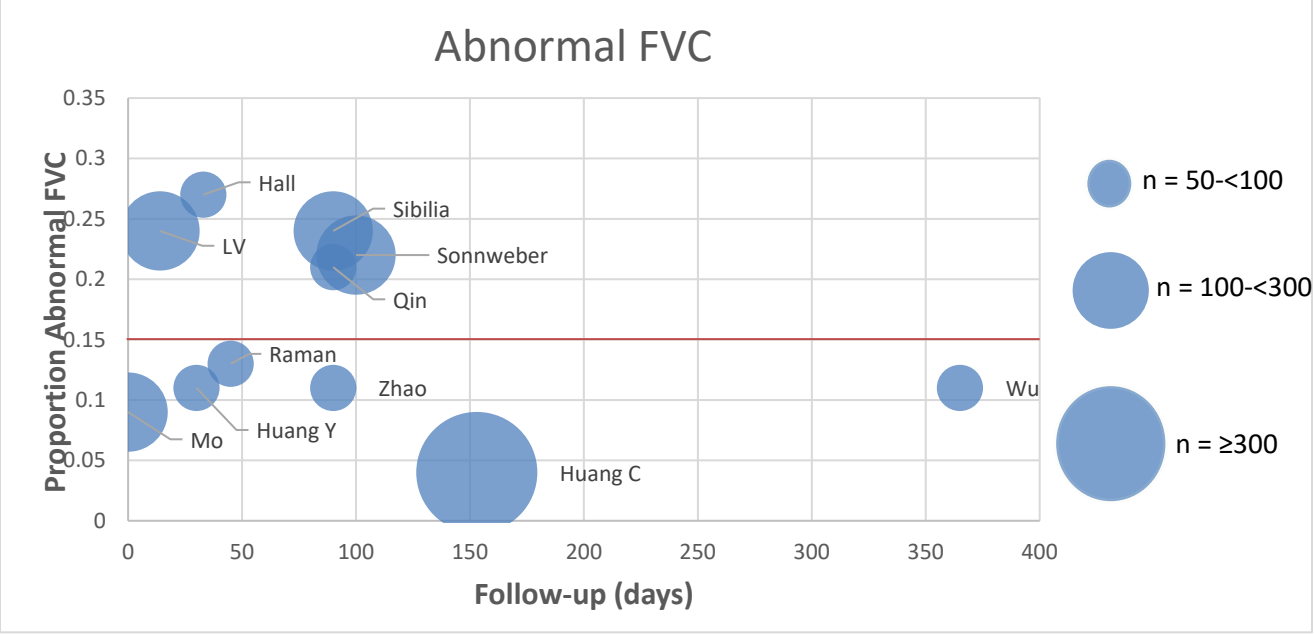
[c]Scale 3=no supplemental oxygen; Scale 4=requiring supplemental oxygen; Scale 5-6=requiring high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation

Figure 3. Abnormal Spirometry – FEV_1[a]



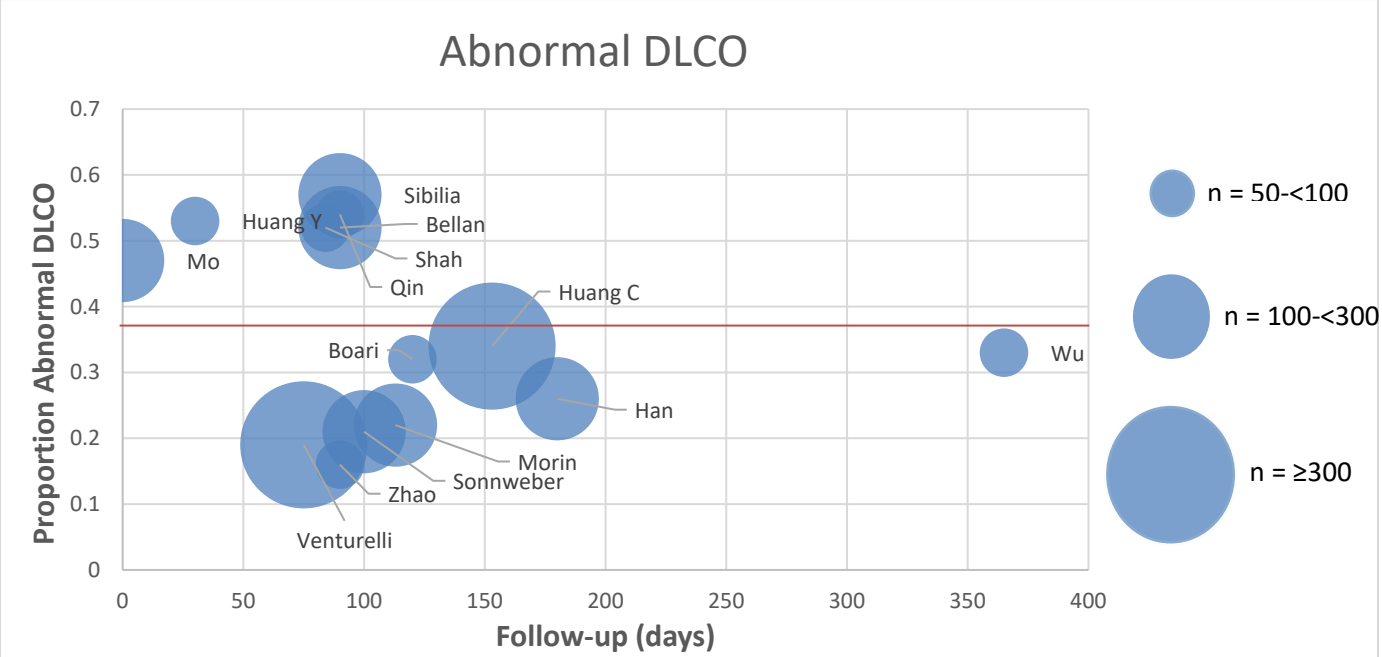
[a]Studies of n≥50; abnormal defined as <80% predicted for most studies (see table below); red line indicates random effects pooled estimate

Figure 4. Abnormal Spirometry – FVC[a]



[a]Studies of n≥50; abnormal defined as <80% predicted for most studies (see table below); red line indicates random effects pooled estimate

Figure 5. Abnomal DLCO[a]



[a]Studies of n≥50; abnormal defined as <80% predicted for most studies (see table below); red line indicates random effects pooled estimate

Five studies provided more detail on the abnormal findings. One study reported a restrictive pattern in 8% (4/50 enrolled patients), restriction with altered diffusion capacity in 18% (9/50), and altered diffusion capacity only in 26% (13/50).[60] The study by Huang further described the observed pulmonary dysfunction as obstructive in 11% (6/57), restrictive in 12% (7/57), and combined obstructive and restrictive in 4% (2/57).[63] Ramani et al reported obstruction in 15% (4/26), restriction in 19% (5/26), and mixed obstruction and restriction in 4% (1/26).[91] The fourth study reported 17% (3/18) with obstructive and 17% (3/18) with restrictive ventilatory impairment.[73] Venturelli reported pulmonary obstruction in 4% (27/716) and pulmonary restriction in 12% (85/716).[132]

Dyspnea

Measures of dyspnea were reported in 26 studies (Table 6). Eight used a modified Medical Research Council (mMRC) measure (https://mrc.ukri.org/research/facilities-and-resources-for-researchers/mrc-scales/mrc-dyspnoea-scale-mrc-breathlessness-scale/) where:

Grade 1 indicates not troubled by breathlessness except on strenuous exertion
Grade 2 indicates short of breath when hurrying on the level or walking up a slight hill
Grade 3 indicates having to walk slower than most people on the level or having to stop after a mile or so (or after ¼ hour) on the level while walking at self-selected pace
Grade 4 indicates having to stop for breath after walking about 100 yards (or after a few minutes) on the level
Grade 5 indicates too breathless to leave the house, or breathless after undressing.

Assessment of dyspnea varied across studies – both the time of assessment post-discharge and the method of assessment (including different cut points for the mMRC). In studies assessing dyspnea at or within 1 month of discharge, reported prevalence ranged from 10-100%. In studies assessing dyspnea beyond 1 month post-discharge, prevalences ranged from 2-81%.

Studies with Control Groups

In studies with control groups, dyspnea was more prevalent[124] or Veterans were at greater risk for dyspnea[104] in the COVID-19 groups than in the control groups.

Table 6. Dyspnea Findings (shaded rows indicate studies added for September 2021 update; Author, Year in bold indicates study with comparator group)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Assessment	Dyspnea
Fuglebjerg, 2020[29] Denmark	ICU admission: 31%	Discharge	Borg Scale following 6 min walk test	Generally <3 on 10-point scale ("moderate" dyspnea)[b]
Curci, 2020[27] Italy	ICU admission: 100%	Admission to rehabilitation unit	mMRC	Grade 4: 13% (4/32) Grade 5: 88% (28/32)
Osikomaiya, 2021[122] Nigeria	42% moderate or severe	15 days post-discharge (median)	Dyspnea (symptom)	10% (25/274)
Karaarsian, 2021[118] Turkey	ICU admission: 0%	14 and 30 days post-discharge	Shortness of breath (symptom)	14d: 38% (114/300) 30d: 26% (78/300)
De Lorenzo, 2020[82] Italy	ICU admission: 3%	22 days post-discharge (median)	mMRC	Mild: 25% (31/126) Moderate: 3% (4/126) Severe: 2% (3/126) Very Severe: 2% (2/126)
Sami, 2020[94] Iran	ICU admission: 8%	30 days post-discharge	Dyspnea (symptom)	Non-severe: 15% (59/400) Severe: 19% (10/52)
Jacobs, 2020[117] USA	95% mild	35 days post-discharge	Shortness of breath (symptom)	45% (58/128)
Tomasoni, 2021[130] Italy	NR	46 days post-discharge (median)	Dyspnea (symptom); on-going	7% (7/105)
Daher, 2020[81] Germany	100% severe	42 days post-discharge (median)	Dyspnea (symptom questionnaire)	33% (11/33)
Raman, 2021[124] United Kingdom	100% moderate to severe	48 days post-discharge (median)	mMRC ≥2	COVID-19: 64% (36/56) Community controls: 10% (3/29) P<.001
Sonnweber, 2020[96] Austria	ICU admission: 22%	63 days 103 days post-diagnosis (mean)	mMRC 3-4	63d: 2% (3/145) 103d: 4% (5/133)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Assessment	Dyspnea
Spinicci, 2021[127] Italy	59% severe or critical	60 days post-discharge (median)	Dyspnea (symptom)	30% (30/100)
Venturelli, 2021[132] Italy	ICU admission: 9%	81 days post-discharge (median)	mMRC	Grades 1-4: 30% (228/767) Grade 1: 23% (176/767) Grade 2: 6% (42/767) Grade 3: 1% (10/767) Grade 4: 0% (0/767)
Wu, 2021[133] China	100% severe	98 days 189 days 275 days 348 days post-discharge (medians)	mMRC ≥1	98d: 81% (67/83) 189d: 30% (25/83) 275d: 12% (10/83) 348d: 5% (4/83)
Shah, 2020[95] Canada	NR	90 days post-symptom onset	Dyspnea (symptom)	21% (12/60)
Qin, 2021[103] China	49% severe	90 days post-discharge	Dyspnea (symptom)	9% (56/647) Non-severe: 7% Severe: 12%
Sibilia, 2021[144] Spain	71% severe	101 days post-discharge (mean)	Dyspnea (symptom)	40% (68/172)
Suarez-Robles, 2021[128] France	ICU admission: 1%	90 days post-discharge	Dyspnea (symptom)	40% (54/134)
Bellan, 2021[107] Italy	ICU admission: 12%	90-120 days post-discharge	Dyspnea (symptom)	6% (13/238)
Garrigues, 2020[61] France	ICU admission: 20%	111 days post-discharge (mean)	mMRC Grade 2 or more	29% (35/120) Ward: 28% ICU: 33%
Morin, 2021[120] France	ICU admission: 30%	113 days post-discharge (median)	Dyspnea (symptom); new onset during or after hospitalization and persisting at time of assessment	16% (78/478)
Boari, 2021[108] Italy	NR	120 days post-discharge	"Effort dyspnea" (questionnaire)	36% (33/91)
Hall, 2021[115] United Kingdom	ICU admission: 39%	28-42 days post-discharge	mMRC; persistent reduction of ≥2 points from self-rated pre-illness score	18% (36/200)
Huang C, 2021[85] China	ICU admission: 4%	153 days post-discharge (median)	mMRC ≥1	26% (419/1615)
Al-Aly, 2021[104] USA (Veterans)	ICU admission: 26%	150 days post-discharge (median)	Shortness of breath (ICD-10) (incident)	HR 1.14 (95%CI 1.04, 1.26) vs seasonal influenza control group

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Assessment	Dyspnea
Han, 2021[116] China	100% severe	175 days post-disease onset (mean)	"Slight exertional" dyspnea	14% (16/114)

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]Study also reported presence of exercise-induced hypoxia (defined as SpO_2 <90%) in 50% (13/26); 6 of the patients underwent further testing and pulmonary embolism was confirmed in 67% (4/6)

Other Pulmonary Outcomes

Studies with Control Groups

In patients with moderate to severe COVID-19 who completed a symptom-limited cardiopulmonary exercise test on a bicycle ergometer at a median of 48 days post-discharge, peak oxygen consumption less than 80% of predicted maximum was reported in 55% (28/51) of the COVID-19 group and 7% (2/27) of the non-COVID control group (P<.001).[124]

Studies without Control Groups

A study of patients admitted to a rehabilitation unit following hospitalization (with ICU admission) for COVID-19 reported that 41% (13/32) required oxygen via nasal cannula, 13% (4/32) required an oxygen mask, and 25% (8/32) required a Venturi mask at admission.[27] A study of patients referred for clinical signs of dysphagia during hospitalization for COVID-19 reported no new cases of aspiration pneumonia.[143] Length of follow-up was not reported.

CARDIOVASCULAR OUTCOMES

Key Findings

In studies with control groups, patients with COVID-19 were at greater risk for post-discharge incident cardiovascular disease outcomes (including acute myocardial infraction, coronary disease, and heart failure) compared to controls. Prevalences of new cardiovascular events ranged from approximately 1 to 3% of the COVID-19 groups and less than 1% in the control groups (k=3).

Myocardial inflammation/fibrosis was more prevalent in COVID-19 patients than controls (k=3). Pericardial effusion was reported in 0% to 20% (k=6). Impairment in left ventricular ejection fraction (LVEF) was noted in 0 to 22% (k=8).

Overview of Studies

Cardiovascular outcomes were reported in 22 studies (Appendix C, Tables 1 and 4) – 9 from Europe,[66,81,82,96,111,120,123,127,131] 4 from the US,[104,110,112,114] 4 from the UK,[57,106,115,124] 3 from China,[62,99,135] and 2 from the Middle East.[24,75] Sample sizes range from 26 to 28,335 COVID-19 patients, mean or median ages ranged from 38 to 70 years, and the percentage of males enrolled ranged from 38% to 94%. Six studies reported race. A history of CVD or CAD was reported in 0% to 40% (15 studies) with a history of hypertension in 5% to 59% (17 studies). Severity of COVID-19 was reported in 7 studies, with 2 enrolling only patients with severe or critical

COVID-19 and 2 studies excluding severe cases. Seven studies included comparison groups.[62,66,99,104,106,110,124]

Cardiovascular Disease

Studies with Control Groups

Three large database studies reported diagnoses of cardiovascular disease following hospitalization for COVID-19. A study of over 27,000 US Veterans reported hazard ratios (HR) for incident acute coronary disease (HR 1.3 [95%CI 1.1, 1.5]) and heart failure (HR 1.2 [95%CI 1.03, 1.4)]) for the COVID-19 group versus individuals hospitalized with seasonal influenza.[104] Outcomes were assessed during the 6 months following COVID-19 infection.

A second study from the US, including over 36,000 individuals in COVID-19 and non-COVID control groups, reported new diagnoses over 4 months following acute COVID-19 infection.[110] Coronary disease (including myocardial infarction, acute coronary syndrome, and cardiogenic shock) was reported in 1.05% of the COVID-19 group and 0.18% of the control group (P<.001). Congestive heart failure was reported in 1.54% of the COVID-19 group and 0.20% of the control group (P<.001). The incidence of myocarditis did not differ between groups (COVID-19: 0.09%, Control: 0.01%).

A study from the UK reported major adverse cardiovascular events (MACE) during a mean of approximately 146 days post-discharge.[106] Included were heart failure, myocardial infarction, stroke, and arrhythmia. New onset events were reported in 2.6% (945/36,130) of the COVID-19 group and 0.5% (190/36,130) of the general population (non-COVID) control group. The difference was statistically significant (P<.001).

Studies without Control Groups

Several smaller studies without control groups also reported cardiovascular diagnoses. A study from the US reported no cases of acute myocardial infarction among 367 individuals hospitalized for COVID-19 at a median of 49 days follow-up.[112] Another US study reported non-ST-segment myocardial infarctions in 0.8% (4/447) within 30 days of hospital discharge.[114] A study from Italy reported "heart failure and other cardiac conditions" in 5% (5/100).[127] A study from the UK identified "previously undiagnosed or deterioration of existing" cardiac causes for ongoing symptoms of breathlessness at 4 to 6 weeks post-discharge in 4% (8/200 enrolled) or 10% (8/81 experiencing breathlessness).[115] Another study from the UK reported evidence of myocarditis in 22% (8/37) at a median of 105 days after COVID-19 diagnosis.[57] A study from China reported newly detected atrial fibrillation in 1% (1/97) at a median of 11 days post-discharge.[135]

Ejection Fraction

Seven studies used echocardiography to assess left ventricular ejection fraction (LVEF).

Studies with Control Groups

Only 1 study included a control group.[124] The authors reported that left ventricular function was normal and comparable between the COVID-19 group and a community-dwelling non-COVID group.

Studies without Control Groups

Another study assessed LVEF at admission and at 6 weeks follow-up.[81] Findings were normal for 94% (17/18) of patients with severe COVID-19 on admission and 88% (29/33) at 6 weeks. In another study, with COVID-19 severity not reported, LVEF was less than 52% in 22% (18/81) of COVID-19 patients at 1.5 months post-discharge.[111] Another study reported LVEF <53% for 3% (4/145) at both 60 days and 100 days post-discharge.[96] In this study, 75% of study participants were hospitalized. In the fourth study, 12% (10/83) had LVEF <50% at a median of 125 days post-discharge.[120] It was noted that no patient had an LVEF <40%. In a study of non-severe COVID-19 patients, LVEF<50% was reported for 1% (1/97) at a median of 11 days post-discharge.[135] A study from Romania enrolled a select group of volunteers under age 55 without prior history of cardiovascular disease.[131] At 6 to 10 weeks post-discharge, diastolic dysfunction was reported in 17% (21/125) and both diastolic dysfunction and impaired left ventricular systolic function was reported in 9% (11/125).

A study from the United Kingdom reported LVEF, assessed with cMRI, for 37 previously hospitalized patients at a median of 105 days after COVID-19 diagnosis.[57] Impairment (≤51%) was noted in 11% (4/37).

Fibrosis and/or Inflammation by Cardiovascular Magnetic Resonance Imaging (cMRI)

Studies with Control Groups

Three studies used cMRI to assess myocardial injury. In a study from Germany, 100 patients were assessed at a median of 71 days following diagnosis.[66] Thirty-three had been hospitalized. The mean age of the patients was 49 years and 53% were male. Among the hospitalized patients, 2 underwent mechanical ventilation and 17 underwent non-invasive ventilation. The study also reported imaging findings for 50 healthy controls and 57 risk factor-matched controls. 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<.05) in the COVID-19 patients than in the healthy controls (0%) or the risk factor-matched controls (17% (9/57)). Pericardial LGE was significantly more prevalent (P<.05) in the COVID-19 patients than in the healthy controls (0%) but not compared with the risk factor-matched controls (14% (8/57)). Abnormal native T1 values were observed in 73% (73/100) of all COVID-19 patients, with significantly higher values (P=.008) in those who had required hospitalization, although the difference was characterized as small. Reporting of T1 and T2 abnormalities, which generally reflect myocardial inflammation, indicated that abnormal native T1 was reported in 12% (6/50) of the healthy controls and 58% (33/57) of the risk factor-matched controls (both P<.05 vs the COVID-19 group). Abnormal native T2 values were observed in 60% (60/100) of the COVID-19 group with no difference between hospitalized and non-hospitalized patients. Prevalences were 12% (6/50) and 26% (15/57) in the healthy controls and risk factor-matched groups, respectively (both P<.05 vs the COVID-19 group).

A second study, from the UK, enrolled patients with moderate to severe COVID-19.[124] Outcomes were assessed at a median of 48 days post-discharge. A matched control group of community-dwelling, non-COVID individuals was included. LGE was observed in 12% (6/52) (myocarditis pattern) of the COVID-19 group and 7% (2/28) of the control group, with

pericardial LGE in 2% (1/52) of the COVID-19 group and 0% (0/28) of the control group. The differences between groups were not statistically significant for either measure. Abnormal native T1 (basal myocardium) was observed in 26% (13/50) in the COVID-19 group and 4% (1/28) in the control group (P=.015). The differences between the COVID-19 and control groups for abnormal native T1 mid-myocardium (COVID-19: 8%, Control 0%) and abnormal apical myocardium (COVID-19: 2%, Control 4%) did not reach statistical significance.

The third study, from China, evaluated 26 patients referred for CMR due to cardiac symptoms post-discharge.[62] Patients with a history of coronary artery disease or myocarditis were excluded. COVID-19 was reported as severe for 15% (4/26) and moderate for 85% (22/26). The study reported data from healthy controls (similar age and gender with no cardiovascular disease or systemic inflammation) who underwent CMR at the same hospital. CMR for the COVID-19 patients was completed at a median of 47 days after the onset of cardiac symptoms. Myocardial edema was noted in 54% (14/26). Of the 14 with edema, 50% (7/14) had positive LGE and 50% (7/14) had a small pericardial effusion. A total of 8 patients (1 without myocardial edema) had positive LGE. Native T1, T2, and extracellular volume (ECV) were significantly elevated in the recovered COVID-19 patients with positive CMR findings compared with the healthy controls.

Pericardial Effusion

Six studies reported pericardial effusion.

Studies with Control Groups

The study from Germany, described above, used CMR imaging and reported pericardial effusion (>10 mm) in 20% (20/100) of the COVID-19 patients, 0% of the healthy controls, and 7% (4/57) of the risk factor-matched controls.[66] The difference between the COVID-19 group and the other groups was statistically significant (P<.05). The UK study, also described above, reported pericardial effusion (>10 mm) in 2% (1/52) of the COVID-19 group and 0% (0/28) of the community-dwelling, non-COVID control group.[124]

Studies without Control Groups

Four studies used ultrasound to assess pericardial effusion. Two studies, both from Saudi Arabia, included only patients admitted to the ICU. One reported pericardial effusion at hospital discharge in 2% (1/64)[24] while the second reported rates of 16% (20/127) at 2 months and 11% (14/127) at 4 months.[75] The third study, from Austria, reported pericardial effusion at 60 days (6% [8/145]) and 100 days (1% [1/134]) in patients, the majority of whom did not require ICU admission.[96] The fourth study, conducted in Germany, reported no pericardial effusion at a median of 6 weeks in patients who did not require mechanical ventilation.[81]

High Sensitivity Troponin T (hsTNT)

Studies with Control Groups

The CMR study from Germany also reported blood test results.[66] Detectable hsTNT (>3 pg/mL) was reported in 71% (71/100) of the COVID-19 group, with significantly elevated hsTNT (>13.9 pg/mL) in 5% (5/100). The mean hsTNT value was significantly lower (P=.002) in patients who recovered at home compared with those who were hospitalized; the difference was described as small. The percentage of patients with detectable hsTNT was significantly higher (P<.05) in the

COVID-19 group than the healthy controls (22% [11/50]) or risk factor-matched controls (54% [31/57]). The UK study, with a control group of non-COVID-19 community members (*ie,* not hospitalized) reported no cases of abnormal troponin T in either the COVID-19 (moderate to severe disease) or control groups at a median of 48 days following discharge.[124]

Studies without Control Groups

Two additional studies reported abnormal troponin T. A study of individuals attending a COVID-19 outpatient clinic 6 weeks post-discharge reported "elevated" troponin T in 19% (15/81).[111] A study of individuals with non-severe COVID-19 referred to an infectious disease clinic and invited to participate, reported elevated troponin T (greater than the 99th percentile of the upper reference limit) in 6% (6/97) at a median of 11 days post-discharge.[135] Individuals with elevated troponin or electrocardiogram abnormalities underwent cMRI. There was no evidence of acute myocarditis in that subgroup.

Other Findings

Studies with Control Groups

A study from China reported newly diagnosed hypertension in 1% (7/538) of the COVID-19 group and 0% (0/184) of a non-COVID-19 control group quarantined at home for greater than 3 months.[99]

Studies without Control Groups

A study from Turkey used echocardiography to identify left ventricular global longitudinal strain (LV-GLS).[123] LV-GLS greater than -18%, an indicator of subclinical myocardial deformation, was observed in 38% (28/74) at a mean of 30 days post-discharge. This included 57% (16/28) of a group with myocardial injury based on troponin level during hospitalization and 26% (12/46) with no myocardial injury. Two studies reported outcomes related to hypertension. A study from Italy reported uncontrolled blood pressure requiring a change in medication in 21% (26/126) at a median of 22 days post-discharge.[82]

NEUROMUSCULAR OUTCOMES

Key Findings

Post-discharge, the prevalence of, or risk for, stroke was higher in COVID-19 groups than in matched control groups (k=2). The incidence of dementia or Alzheimer's post-COVID-19 was low but may exceed that of non-COVID cases.

Several studies reported on cognitive function with most indicating some dysfunction. In 5 studies using established assessment tools with specified thresholds, cognitive impairment was observed in 23% to 57%. One of the studies included a community-based control group and reported no statistically significant difference between the COVID-19 and control groups. Cognitive symptoms including attention deficits, confusion, and memory difficulty were reported in 5% to 34% of COVID-19 patients (k=9). In 2 additional studies with control groups, memory problems were more frequently reported in the COVID-19 groups.

In patients hospitalized for stroke and testing positive for COVID-19, a "good" prognosis based on modified Rankin Scale scores at the time of discharge was reported in 17% to 60% (k=6).

Overview of Studies

Thirty studies reported neurological outcomes (Appendix C, Tables 1 and 5). Twelve were conducted in Europe,[25,61,81,82,105,111,120,125,127,130,132,142] 10 in the US,[31,33,77,91,104,109,110,114,117,129] 3 in multiple nations,[23,36,48] 2 in the UK,[53,124] and 1 each in the Middle East,[39] India,[46] and Africa.[122] Sample sizes ranged from 13 to 236,279 COVID-19 patients, mean or median ages ranged from 42 to 76 years, and between 39% and 94% were male. In 13 studies reporting race, 14% to 80% were White, 0% to 40% were Black, 6% to 57% were Hispanic, and 0% to 19% were Asian. Six studies reported on severity of COVID-19 with 3% to 62% of enrollees with severe or critical COVID-19. Ten studies included a comparison group (either concurrent non-COVID-19 or pre-COVID-19 patients).

Stroke and Other Diagnoses

Studies with Control Groups

The large database study of US Veterans without a history of stroke in the past year reported the hazard ratio (HR) for stroke in the 6 months following COVID-19 infection vs a matched control group consisting of individuals hospitalized for seasonal influenza was 1.30 (95%CI 1.05, 1.60).[104] Another US database study, with a non-COVID control group, reported the prevalence of new onset stroke during the 4 months after acute illness.[110] Ischemic and hemorrhagic stroke was reported in 1.12% of the COVID-19 group and 0.29% of the matched non-COVID control group (risk difference 0.83% [95%CI 0.4, 1.2], P<.001). A US study, without a control group for the subgroup of patients hospitalized, reported a first ischemic stroke in 6 months following COVID-19 in 1.6% (741/46,302) and a first intracranial hemorrhage in 0.6% (292/46,302).[129]

For incident neurocognitive disorders, US Veterans hospitalized for COVID-19, compared to hospitalized seasonal influenza cases, had an excess burden of 16.2 (95%CI 10.4, 21.2) per 1000 COVID-19 persons at 6 months.[104] In another large database study, the odds ratios for neurocognitive disorders (vs hospitalized non-COVID control patients) were 1.6 (95%CI 1.2, 2.1) in the first 30 days after discharge.[109] The odds ratios were not statistically significant at 60, 90, or 120 days.

In a large database study from the US, dementia was newly diagnosed in 0.23% of the COVID-19 group and 0.03% of the non-COVID control group (risk difference 0.2% [95%CI 0.7, 0.3], P<001) at 4 months after-acute illness.[110] In the same study, Alzheimer's disease was reported in 0.04% of the COVID-19 group and 0% of the control group (P<.001).

Studies without Control Groups

A study from the US reported 1 case of ischemic stroke (0.22% [1/447]) in 30 days post-discharge.[114] A study from Denmark reported stroke in 4% (2/45) of patients with 3 month follow-up data.[142] A study from Austria reported stroke with clinical symptoms at 3 months post-discharge (not diagnosed before COVID-19) in 1% (1/135).[125]

A US study, without a control group for the subgroup of patients who were hospitalized, reported the incidence of dementia at 6 months post-discharge was 1.5% (676/46,302).[129]

Other disease diagnoses reported included "any" neurological disease (not diagnosed before COVID-19) in 15% (20/135) at 3 months,[125] encephalopathy in 2% at 3 months,[125,142] and Parkinsonism in 0.2% to 1.0% at 3 or 6 months.[125,129]

Brain Imaging

A study from the UK, with a community-dwelling control group, reported brain abnormalities on MRI in 24% (13/54) in the COVID-19 group and 21% (6/28) in the control group (P=.79) at a median of 1.6 months post-discharge.[124] Of the abnormalities noted, 2 in the COVID-19 group and none in the control group were hemorrhagic or ischemic abnormalities.

NIH Stroke Scale

Two studies, both with control groups, reported NIH Stroke Scale scores at discharge.[25,31] Scores range from 0 (no symptoms) to 42 (severe symptoms) with scores between 1 and 4 indicating minor stroke symptoms and scores between 5 and 15 indicating moderate stroke symptoms (https://www.stroke.nih.gov/resources/scale.htm). The study from Italy, enrolling patients admitted primarily for neurological disease, reported median [IQR] scores of 9.0 [1.0-19.0] in the COVID-19 group and 2.0 [0.0-6.8] in the non-COVID-19 group (P=.005).[25] The study from the US reported median [IQR] scores of 11 [4-23] in the overall study group of 13 patients (6 admitted for COVID-19 symptoms who experienced a stroke during hospitalization, 7 admitted for stroke and testing positive for COVID-19) and 3 [2-13] in the non-COVID comparison group.[31]

Cognitive Impairment

Nine studies used established instruments to clinically assess cognitive impairment (Table 7).[82,91,105,111,120,124,125,130,132] Studies including at least 50 COVID-19 patients are shown on Figure 6.

Based on scores from the Montreal Cognitive Assessment (MoCA) at approximately 22 to 90 days post-discharge, between <1% and 73% had cognitive deficits. In the 4 studies specifying a cut-point of 24 to 26, deficits were noted in 23% to 57%. In 2 studies using the Mini Mental State Examination (MMSE), cognitive deficits were observed in 20%[105] and 40%[130] of the COVID-19 patients. Similar findings were observed in 2 studies using other cognitive instruments.

Studies with Control Groups

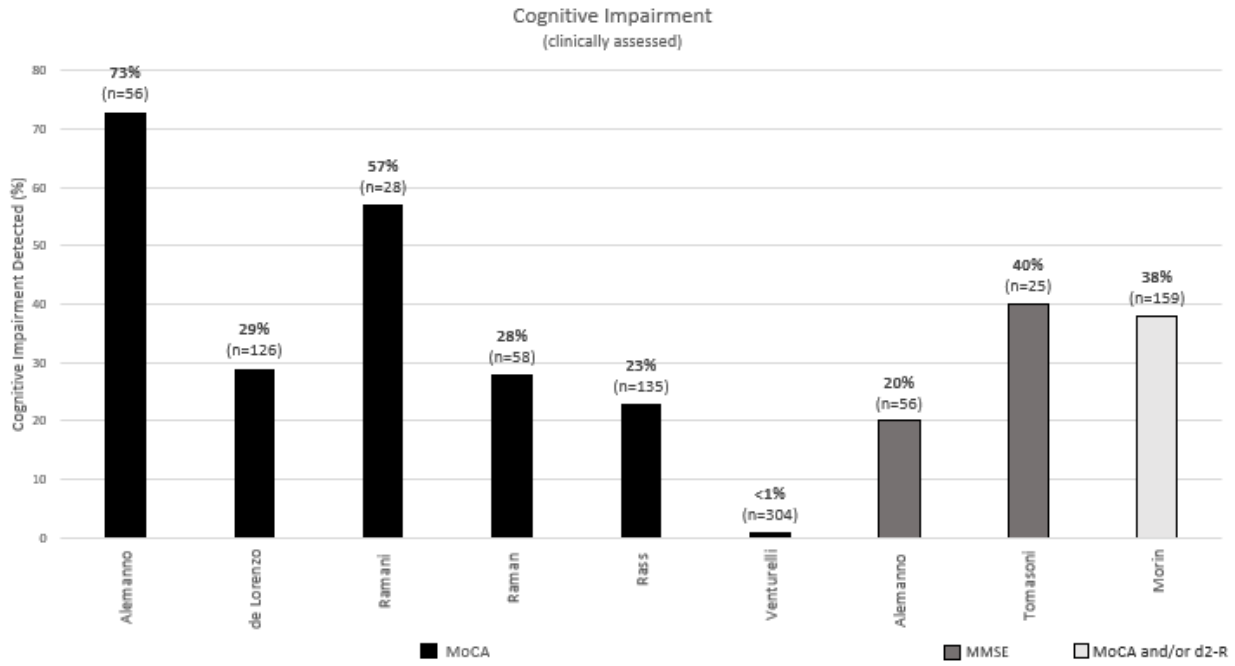
One of the 4 studies specifying a cut-point for the MoCA included a community-based control group and reported scores of less than 26 in 28% of the COVID-19 group and 17% of the control group (P=.30).[124]

Table 7. Clinical Assessment of Cognitive Impairment (shaded rows indicate studies added for September 2021 update; Author, Year in bold indicates study with comparator group)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Cognitive Impairment
MMSE			
Alemanno, 2021[105] Italy	NR	30 days post-discharge	"Deficits"[b] 20% (11/56) (all mild or moderate)
Tomasoni, 2021[130] Italy	NR	46 days post-discharge (median)	40% (10/25) (MMSE<25)
MoCA			
De Lorenzo, 2020[82] Italy	ICU admission: 3%	22 days post-discharge (median)	29% (36/126) (MoCA <24)
Alemanno, 2021[105] Italy	NR	30 days post-discharge	"Deficits"[b] 73% (41/56)
Ramani, 2021[91c] US	NR	40 days post-discharge (median)	57% (16/28) (MoCA <26)
Raman, 2021[124] United Kingdom	ICU admission: 36%	48 days post-discharge (median)	28% (16/58) (MoCA <26) Community controls: 17% (5/30) P=.30
Venturelli, 2021[132] Italy	ICU admission: 9%	81 days post-discharge (median)	0.66% (2/304) ("Pathologic")
Rass, 2021[125] Austria	23% severe	90 days post-discharge	23% (29/135) (MoCA<26)
Other Instruments			
de Graaf, 2021[111] Netherlands	ICU admission: 42%	42 days post-discharge	CFQ: 27% (13/48) IQ-CODE-N: 26% (10/38)
Morin, 2021[120] France	ICU admission: 30%	113 days post-discharge (median)	MoCA or d2-R: 38% (61/159)

Abbreviations: CFQ=Cognitive Failures Questionnaire; IQ-CODE-N=Informant Questionnaire on Cognitive Functioning in the Elderly; MMSE=Mini Mental State Examination; MoCA=Montreal Cognitive Assessment
[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]Cut-points for "deficits" not defined
[c]Study enrolled fewer than 50 and is not included on the figure below

Figure 6. Cognitive Impairment



Cognitive Symptoms

Eleven studies used self-report assessments of cognitive symptoms (Table 8).[61,81,104,110,117,120,122,125,127,130,132] Studies including at least 50 COVID-19 patients are shown on Figure 7. One study reported a composite measure of at least 1 cognitive complaint as well as individual measures of concentration problems, mental slowness, and memory difficulties.[120] Only the composite measure is shown on Figure 7.

Studies with Control Groups

Two large database studies included control groups. A study of over 26,000 US Veterans reported higher risk of memory problems over 6 months following COVID-19 infection (HR 1.42 [95%CI 1.23, 1.63]) in the COVID-19 group compared to a matched control group hospitalized for seasonal influenza.[104] A second US study with data from over 36,000 individuals reported amnesia/memory difficulty in 2.9% of the COVID-19 group and 0.4% of the matched non-COVID control group in the 4 months after acute illness (P<.001).[110]

Studies without Control Groups

In studies without control groups, attention deficits were noted in 5% to 27%, cognitive deficits in 18% to 21%, confusion in 5% to 10%, and memory difficulties in 17% to 34%.

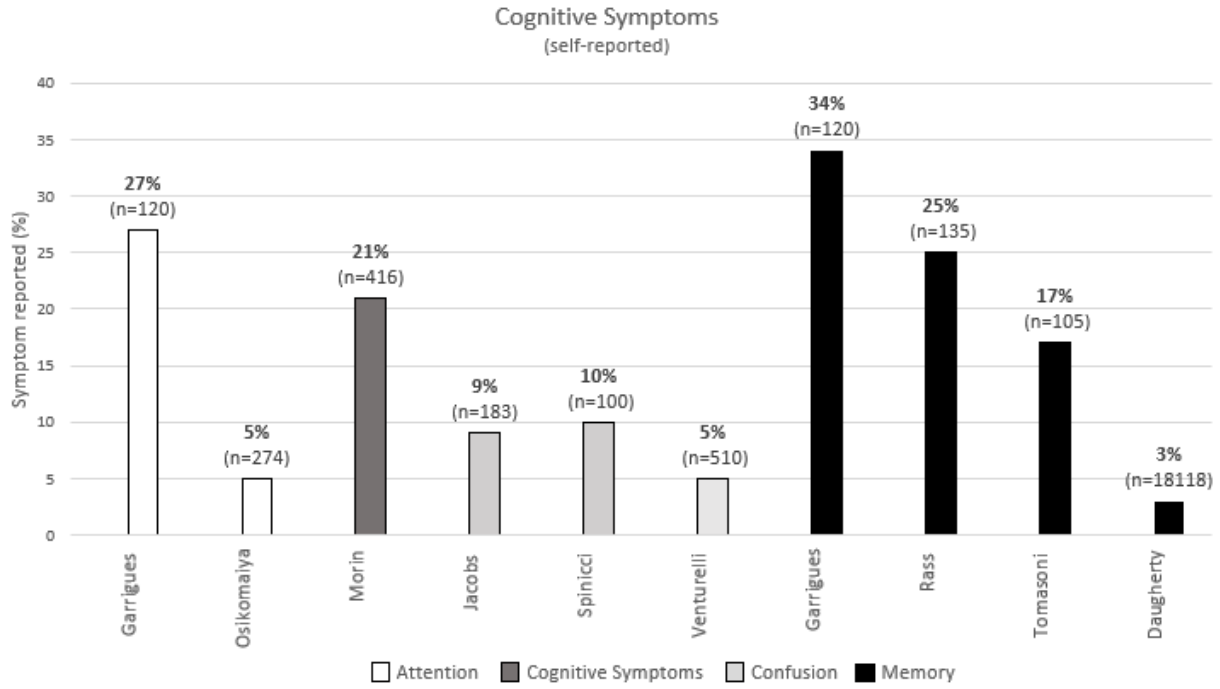
Table 8. Cognitive Symptoms (shaded rows indicate studies added for September 2021 update)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Findings
Attention Deficits			
Osikomaiya, 2021[122] Nigeria	3% severe	15 days post-discharge (median)	Attention or Memory Deficit: 5% (14/274)
Garrigues, 2020[61] France	ICU admission: 20%	111 days post-discharge (mean)	27% (32/120)
Morin, 2021[120b] France	ICU admission: 30%	113 days post-discharge (median)	Concentration Problems: 10% (41/412)
Cognitive Deficits			
Daher, 2020[81c] Germany	100% severe (inclusion criteria)	42 days post-discharge (median)	Cognitive Disorders (not defined): 18% (6/33)
Morin, 2021[120b] France	ICU admission: 30%	113 days post-discharge (median)	At Least 1 Cognitive Complaint (Memory, Mental Slowness, or Concentration): 21% (86/416) Mental Slowness: 10% (42/415)
Confusion			
Jacobs, 2020[117] US	NR (95% mild)	35 days post-discharge	9% (16/183)
Spinicci, 2021[127] Italy	59% severe or critical	60 days post-discharge (median)	10% (10/100)
Venturelli, 2021[132] Italy	ICU admission: 9%	81 days post-discharge (median)	5% (23/510)
Memory Difficulty			
Tomasoni, 2021[130] Italy	NR	46 days post-discharge (median)	Memory Disorder: 17% (18/105)
Rass, 2021[125] Austria	23% severe	90 days post-discharge	Forgetfulness, Trouble Concentrating, Difficulty Thinking: 25% (30/135)
Garrigues, 2020[61] France	ICU admission: 20%	111 days post-discharge (mean)	34% (41/120)
Morin, 2021[120b] France	ICU admission: 30%	113 days post-discharge (median)	Memory Difficulties: 18% (73/416)
Daugherty, 2021[110] US	ICU admission: 13%	120 days post-acute	Amnesia/Memory Difficulty:2.90% Matched control group: 0.43% N=18,118 per group; P<.001

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Findings
		infection (mean)	
Al-Aly 2021[104] USA(Veterans)	ICU admission: 26%	150 days post-discharge (median)	Memory Problems: HR 1.42 (95%CI 1.23, 1.63) vs matched controls hospitalized with seasonal influenza; N>13,000 per group

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]Only the composite measure (at least 1 cognitive complaint) is shown on Figure below
[c]Study enrolled fewer than 50 and is not included on Figure below

Figure 7. Self-reported Cognitive Symptoms



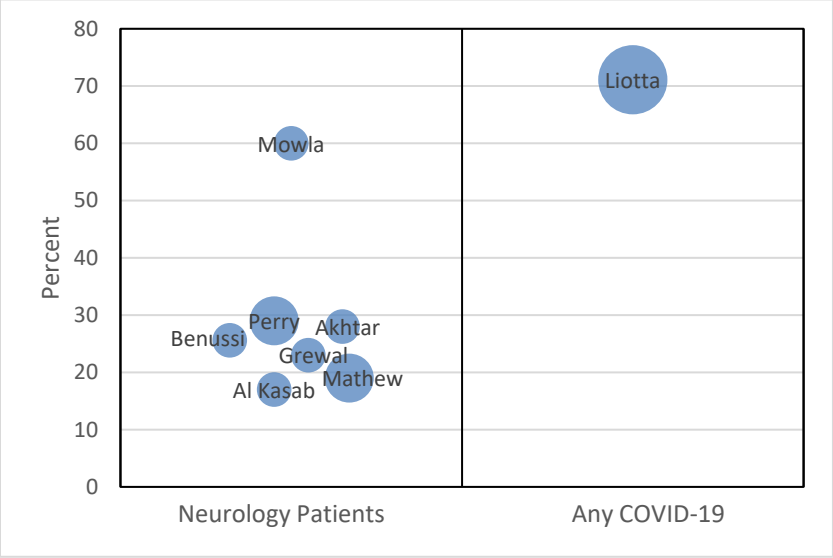
In addition to the studies in Tables 7 and 8, a study of patients who were admitted to home health care following hospitalization for COVID-19 reported that 23% (297/1302) required prompting and 6% (76/1302) required assistance and direction at the time of admission.[77] At discharge from home health care, the values were 10% (130/1302) and 3% (42/1302), respectively. This study also reported confusion in new and complex situations for 41% (536/1302) at admission and 19% (251/1302) at discharge.

Modified Rankin Scale

Eight studies reported modified Rankin Scale (mRS)(Modified Rankin Scale for Neurologic Disability - MDCalc) results at the time of hospital discharge (Figure 8, Table 9). Seven studies were in neurology patients, 6 of which enrolled patients hospitalized for neurological conditions and testing positive for COVID-19 (Table 9). All but 2 included non-COVID control groups.

Based on an mRS score of 0 to 2 being considered a good outcome – individuals are "able to look after their own affairs without assistance" – only 1 of the 7 studies of neurology patients reported that the majority had a good outcome at discharge.

Figure 8. Modified Rankin Scale (mRS) ≤2 ("Good Outcome") at Discharge



[a]Patients with stroke or other neurological manifestations; may have been hospitalized for neurological conditions and then tested positive for COVID-19 or hospitalized for COVID-19 with subsequent neurological diagnoses

LEGEND
Sample Size 0-50 51-100 >100

Table 9. Modified Rankin Scale (mRS) at Discharge – 'Good' Prognosis (Author, Year in bold indicates study with non-COVID comparator group)

Author, Year Country	Population	COVID-19 Severity[a]	'Good" Prognosis at Discharge
Akhtar, 2021[39] Qatar	Hospitalized for stroke	31% requiring mechanical ventilation	28% (9/32) Concurrent Non-COVID group: 52% (112/216) Pre-COVID era group: 60% (348/585) P=.001
Al Kasab, 2020[23] Multi-national	Mechanical thrombectomy post-stroke; symptomatic patients tested for COVID-19	39% requiring mechanical ventilation	17% (2/12) Concurrent Non-COVID group: 30% (94/316) P=.52
Benussi, 2020[25] Italy	Admitted for acute cerebrovascular disease and tested positive for COVID-19	NR	26% (11/43) Non-COVID group: 71% (48/68) P<.001
Grewal, 2020[31] USA	COVID admission followed by stroke (n=6) or stroke admission followed by positive for COVID-19 (n=7)	62% severe/critical	23% (3/13) Concurrent Non-COVID group: 53% (28/53) P=.047

Author, Year Country	Population	COVID-19 Severity[a]	'Good" Prognosis at Discharge
Liotta, 2020[33] USA	With and without neurological manifestations during hospitalization with COVID-19	26% severe	71% (363/509 With neurological manifestations 71% (299/419) No neurological manifestation: 70% (63/90)
Mathew, 2020[46] India	Hospitalized for stroke, testing positive for COVID-19	NR	19% (12/62)
Mowla, 2020[48] Multi-national	Hospitalized for stroke, testing positive for COVID-19	9% severe	60% (6/10) Historical control group: 77% (44/57) P=.26
Perry, 2020[53] United Kingdom	Hospitalized for stroke, testing positive for COVID-19	8% requiring mechanical ventilation	29% (estimated from plot) Concurrent non-COVID group: 46% (estimated from plot)

Abbreviations: NR=not reported
[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity

Another multi-nation study reported severe disability based on mRS scores in 51% (49 of 96 survivors).[36] The median [IQR] scores for the COVID-19 group and a propensity-matched group were 4 [2-6] and 2 [1-4], respectively (P<.001).

Neuromuscular Outcomes

Studies with Control Groups

Two large database studies from the US reported neuromuscular outcomes.[109,129] One reported a significantly greater odds of myopathies at 1 to 30 days post-discharge in the COVID-19 group versus the non-COVID-19 control group (OR 5.9 [95%CI 2.8, 12.4]).[109] The second study reported that 1.2% of patients (574/46,302) experienced myoneural junction or muscle disease in the 6 months following discharge.[129] This study did not include control group data for the hospitalized subgroup.

Studies without Control Groups

A smaller study from Europe reported polyneuropathy at 3 months post-discharge (not diagnosed before COVID-19) in 13% (17/135).[125]

RENAL OUTCOMES

Key Findings

The prevalence of, or risk for, new onset chronic kidney disease and acute kidney injury following hospitalization for COVID-19 was greater than in matched control groups (k=4). Need for renal replacement therapy (RRT) at discharge was reported in 4% to 34% of those who had required RRT during hospitalization (k=5).

Overview of Studies

Renal outcomes were reported by 18 studies (Appendix C, Tables 1 and 6): 10 from the US,[35,49,97,102,104,109,110,121,139,140] 4 from the UK,[57,83,106,124] and 1 each from Europe,[120] Brazil,[145] China,[85] and Japan.[47] Enrollments ranged from 37 to 28,335 with 10 including over 1000. Mean or median ages ranged from 50 to 71, with 38% to 94% male. Twelve studies reported race with 11% to 78% White, 5% to 40% Black, and 9% to 43% Hispanic. A history of chronic kidney disease was reported in 2% to 67% (10 studies) and hypertension in 5% to 89% (14 studies). Only 2 reported COVID-19 severity with 32% and 100% severe. Three studies enrolled only patients admitted to an ICU.

Chronic Kidney Disease (CKD)

Studies with Control Groups

CKD was reported in 3 large database studies.[104,106,110] 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 versus a seasonal influenza control group was 1.4 (95%CI 1.1, 1.7).[104] A second US study, with data from over 36,000 individuals, reported new diagnoses of CKD at 4 months after acute illness in 2.1% of the COVID-19 group and 0.7% of the non-COVID control group.[110] The third study, completed in the UK, with data from over 82,000 individuals, reported new onset CKD in 0.6% of the COVID-19 group and 0.3% of the general population control group at a mean of approximately 146 days post-discharge.[106]

Studies without Control Groups

Three smaller studies reported kidney dysfunction.[120,121,124] A study from France reported persistent alteration of kidney function at approximately 4 months post-discharge in 2% (2/95 who experienced AKI during hospitalization or 0.4% (2/478 overall).[120] Residual renal impairment (not present prior to COVID-19) was observed in 3% (2/58) at 2 to 3 months post-discharge in a study from the UK.[124] The third study, from the US, reported kidney dysfunction at 3-6 months post-discharge in 8% (15/182).[121] The study also reported a HR for kidney recovery by 3-6 months in those who hadn't achieved recovery by the time of hospital discharge (HR 0.6 [95%CI 0.35, 0.92], P=.02).

Acute Kidney Disease (AKD)

Five studies reported acute kidney disease.

Studies with Control Groups

Three database studies reported new diagnoses of acute kidney disease following discharge.[104,109,110] The study of over 27,000 US Veterans reported an adjusted hazard ratio (HR) for acute kidney injury during the 6 months following COVID-19 infection for the COVID-19 group versus a seasonal influenza control group (HR 1.2 (95%CI 1.1, 1.4)).[104] A second US study reported odds ratios (ORs) for acute and unspecified kidney failure versus a hospitalized non-COVID-19 control group.[109] The ORs decreased from 1.3 (95%CI 1.0, 1.6) at 30 days post-discharge to 0.6 (95%CI 0.4, 0.8) at 120 days post-discharge. The third study, also from the US, reported a new diagnosis of acute kidney injury during the 4 months after acute infection in 2.9%

of the COVID-19 group and 0.5% of the non-COVID control group.[110] The risk difference was 2.4 (95%CI 1.7, 3.1).

Studies without Control Groups

A study from the US reported acute kidney disease (AKD) at discharge in 25% (291/832).[102] Twenty-three percent were Stage 1, 6% Stage 2, and 6% Stage 3. AKD stages were defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on creatinine (KI_SuppCover_2.1.indd (kdigo.org)). At a median follow-up of 21 days, data were available for n=77 with AKD at discharge. Of those, 36% (29/77) had recovered, 33% (25/77) were Stage 1, 13% (10/77) were Stage 2, and 18% (14/77) were Stage 3. Data were also available for n=135 who had recovered kidney function at discharge. Of those, 86% (116/135) remained recovered, 10% (14/135) had new Stage 1 AKD, 2% (3/135) had new Stage 2 AKD, and 2% (3/135) had new Stage 3 AKD.

A second study from the US reported on 3,854 individuals who developed acute kidney injury while hospitalized for COVID-19.[35] Among those who required RRT while hospitalized, 17% (108/638) survived. Of the survivors, 33% (36/108) had not recovered kidney function at the time of discharge. Authors reported that 58% (19/33) had underlying chronic kidney disease at hospital admission. Among those who did not require RRT while hospitalized, 52% (1663/3216) survived and 26% (430/1663) of those had not recovered kidney function.

Need for Renal Replacement Therapy (RRT)

Eight studies (none with a control group) reported the need for RRT (Table 10). Between 1% and 34% required RRT at the time of discharge. Two of the studies reported post-discharge data with 7% and 18% continuing to require RRT. Lack of pre-COVID RRT status limits conclusions.

Table 10. Need for Renal Replacement Therapy

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Renal Replacement
Doher, 2020[145] Brazil	ICU admission: 100%	Discharge	11% (1/9)
Gupta, 2020[139] US	ICU admission: 100%	Discharge 60 Days after ICU Admission	34% (73/216 discharged; required RRT during hospitalization) 18% (39/216 discharged; required RRT during hospitalization)
Hamilton, 2020[83] United Kingdom	ICU admission: 16%	Discharge	6% (2/32 who required RRT during hospitalization)
Hittesdorf, 2020[140] US	100% severe	Discharge 90 days after admission	4% (2/45 who required RRT during hospitalization) 7% (2/27 surviving at 90 days
Matsunaga 2020[47] Japan	32% severe	Discharge	1% (16/2,431)
Naar, 2020[49] US	ICU admission: 100%	Discharge	11% (5/46 who required RRT during hospitalization
Ng, 2020[35] US	ICU admission: 92%	Discharge	31% (33/108 who required RRT during hospitalization)

Author, Year Country	COVID-19 Severity[a]	Time of Assessment	Renal Replacement
Stevens, 2020[97] US	ICU admission: 100%	30 days (median) from RRT Initiation (in hospital)	8% (9/115) (NOTE: 2/9 had been discharged)

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity

Imaging Findings

A study from the UK reported an imaging finding at a median of 105 days post-COVID-19 diagnosis.[57] Impairment on kidney cortex T1 was observed in 5% (2/37) with normal findings in 95% (35/37). A study from China reported no abnormal kidney morphology (on ultrasound) at a median of 153 days post-discharge.[85]

ENDOCRINE OUTCOMES

Key Findings

Three large database studies, 1 from the US enrolling Veterans, reported greater risk of new onset diabetes following hospitalization for COVID-19 compared to matched control groups consisting of individuals either hospitalized for seasonal influenza, from the general population, or without COVID-19.

Overview of Studies

Three studies (2 from the US and 1 from the UK) reported endocrine outcomes (Appendix C, Table 7).[104,106,110] All were database studies with 13,654 to 28,335 COVID-19 patients. One study enrolled US Veterans. The mean age was 70 years; 94% were male, 58% were White and 34% were Black.[104] The other study from the US did not report demographic data for the subgroup of patients who were hospitalized for COVID-19.[110] In the study from the UK, 55% were male, 72% were White, 5% were Black, and 9% were Asian.[106] None of the studies reported the percentage with severe or critical COVID-19; between 10% and 25% were admitted to the ICU.

Diabetes

Studies with Control Groups

Three database studies, 2 from the US[104,110] and 1 from the UK,[106] reported the presence of diabetes (Appendix C, Table 1 and 7). One of the US studies, with data from over 27,000 Veterans, reported a greater risk for diabetes in the COVID-19 group than in a matched, seasonal influenza group (HR 1.6 [95%CI 1.36, 1.87]).[104] The findings were based on participants without a history of diabetes in the past year. At 6 months following COVID-19 infection, the excess burden per 1000 hospitalized COVID-19 patients was 21.4 (95%CI 15.1, 26.8). The second US study included over 36,000 hospitalized patients in COVID-19 and matched non-COVID-19 groups. Type 2 diabetes, through 4 months after acute illness, was reported in 3% of the COVID-19 group and 0.8% of the control group (risk difference 2.2% [95%CI 1.4, 3.2]).[110]

The UK study, with data from over 72,000 individuals (COVID-19 and a matched, general population control group) reported new onset 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 the

control group.[106] The rates per 1000 person-years were 28.7 for the COVID-19 group and 8.2 for the control group.

GASTROINTESTINAL OUTCOMES

Key Findings

Large database studies identified an excess burden of incident gastrointestinal disorders in individuals hospitalized for COVID-19 compared to seasonal influenza and a higher incidence of new onset chronic liver disease in individuals hospitalized for COVID-19 compared to non-COVID controls.

Overview of Studies

Six studies reported gastrointestinal outcomes (Appendix C, Table 8) including 2 from the US,[104,110] 2 from the UK,[57,106] and 1 each from Europe[111] and China.[85] Sample sizes ranged from 37 to 28,335 COVID-19 patients; 4 of the 6 studies enrolled more than 1000 individuals. Mean or median age ranged from 50 to 70 years with 38% to 94% male. Three studies reported race with 58% to 76% White and 5% to 34% Black. None of the studies reported COVID-19 severity but between 4% and 42% were treated in the ICU (5 studies).

Gastrointestinal Disease

Studies with Control Groups

Two large database studies identified gastrointestinal disease using ICD-10 codes.[104,106] The study of Veterans identified incident gastrointestinal disorders (*eg,* dysphagia) in over 27,000 individuals hospitalized for either COVID-19 or the seasonal influenza (control group).[104] During 6 months follow-up starting 30 days after COVID-19 diagnosis, the excess burden per 1000 COVID-19 persons was 19.3 (95%CI 12.8, 25.1). The second study, from the UK, identified new onset chronic liver disease over a mean follow-up of 140 days among individuals hospitalized with COVID-19 (0.2% [70/46,395]) and the general population (0.04% [15/46,395]).[106] The difference was statistically significant (P<.001).

Liver Test Findings

Studies with Control Groups

In a US study with over 18,000 individuals in each group, new liver test abnormalities identified during 4 months following acute infection were reported in 3.3% of the COVID-19 group and 1.4% of the non-COVID-19 control group.[110] The risk difference was statistically significant (RD 1.95% [95%CI 1.06, 2.58]).

Studies without Control Groups

A smaller study from the Netherlands with 1.5 months follow-up reported elevated liver enzyme in 2% (2/81).[111]

Imaging Findings

Two studies reported liver imaging abnormalities (Appendix C, Tables 1 and 8). A UK study reported liver inflammation (cT1 in ms) was normal (<784 ms) in 76% (28/36 evaluated) and impaired (≥784 ms) in 24% (9/37) at a median of 105 days after COVID-19 diagnosis.[57] The study from China, reporting outcomes in 1733 patients at a median of 153 days post-discharge, observed no cases of abnormal liver morphology on ultrasound.[85]

HEMATOLOGIC OUTCOMES

Key Findings

Post-discharge VTE was reported in 0% to 14% (k=17). Bleeding events were rare. The prevalence of, or risk for, coagulation disorders was higher in COVID-19 groups than in control groups. Interpretation is limited by varying time points post-discharge (5 days to 153 days), little reporting on prophylactic anticoagulant use, and varying study inclusion criteria (*ie,* assessment of individuals with versus without signs or symptoms of VTE; follow-up of all patients via medical records, outpatient clinics, or telephone contact vs evaluation of patients with suspicion of VTE).

Overview of Studies

Eighteen studies reported hematologic outcomes defined as venous thromboembolism or bleeding events (Appendix C, Tables 1 and 9). Seven studies were from the US,[65,79,84,104,109,110,114] 4 were from the UK,[68,93,98,115] 3 from the Middle East,[24,75,92] 3 from Europe,[81,113,126] and 1 from China.[85] Sample sizes ranged from 9 to 27,284 COVID-19 patients, with 7 studies enrolling more than 1000. Mean or median ages of enrolled patients were 43 to 74 years and 48% to 94% were male. Only 3 studies reported race, with 37% to 58% White and 26% to 34% Black. Two studies from the Middle East enrolled only patients with severe or critical COVID-19 with 100% receiving treatment in the ICU.[24,75] No other studies specified COVID-19 severity but 4% to 42% were treated in the ICU (12 studies).

Thromboembolism

A study from Saudi Arabia reported the incidence of deep venous thrombosis (DVT) based on screening discharge ultrasound was 13% (8/64). All patients had been admitted to intensive care and received mechanical ventilation.[24] None had DVT signs or symptoms.

The other 17 studies reported VTE outcomes post-discharge (Table 11). Three studies included control groups.[104,109,110] Follow-up ranged from a mean of 5 days to a median of 153 days with VTE in 0% to 14.2%.

Table 11. Post-discharge Thromboembolism (shaded rows indicate studies added for September 2021 update; Author, Year in bold indicates study with comparator group)

Author, Year Country	COVID-19 Severity[a]	Anticoagulation at Discharge	Method of Assessment	Follow-up Time	Thromboembolism
Brosnahan, 2020[79]	NR	NR	Re-presented to study hospital or	5 days (mean time	Thrombotic event[b:] 0.46% (9/1,975)

Author, Year Country	COVID-19 Severity[a]	Anticoagulation at Discharge	Method of Assessment	Follow-up Time	Thromboembolism
US			ED with concern for a thrombotic event	to re-presenting)	
Hill, 2020[84] US	Mechanical ventilation: 52%	No routine post-discharge VTE prophylaxis	Medical records	21 days post-discharge (median)	VTE:0.14% (3/2,075)
Vlachou, 2021[98] United Kingdom	NR	100% “severe” (not defined)	Admissions post-discharge	28 days post-discharge	PE:1% (4/370 enrolled)[d]
Hall, 2021[115] United Kingdom	ICU admission: 39%	NR	Follow-up clinic with x-ray and other tests as indicated	28-42 days post-discharge	PE: 2% (4/200)
Patell, 2020[65] US	ICU admission: 26%	0% (excluded from primary analysis)	Medical records (at least 1 post-discharge contact)	30 days post-discharge	PE, intracardiac thrombus, thrombosed arteriovenous fistula, ischemic stroke (1 each): 2.5% (4/163)
Eswaran, 2021[114] US	ICU admission: 39%	43%	Medical records with manual validation	30 days post-discharge	PE: 1% (4/447) Total Events: 2% (9/447)
Chevinsky, 2021[109] USA	ICU admission: 40%	NR	Medical records	Post-discharge 30 days 60 days 90 days 120 days	Acute PE (vs non-COVID controls) OR 1.5 (95%CI 1.0, 2.1) OR 1.4 (95%CI 0.9, 2.1) OR 1.2 (95%CI 0.7, 1.0) OR 1.2 (95%CI 0.7, 2.1)
Roberts, 2020[68] United Kingdom	ICU admission: 11%	0% (thrombo-prophylaxis withdrawn on hospital discharge)	Imaging if suspicion of VTE on re-presentation or primary care referral	42 days post-discharge (median)	VTE: 0.48% (9/1,877) Comparison cohort 0.31% (56/18,159) OR 1.6 (95%CI 0.77, 3.1)
Salisbury, 2020[93] United Kingdom	ICU admission: 16%	0%[a]	Medical records	42 days post-discharge	VTE: 3% (4/152)[c]
Daher, 2020[81] Germany	Mechanical ventilation: 0%	None	Outpatient pulmonary clinic	42 days post-discharge (median)	Thromboembolic event: 0% (0/33)

Author, Year Country	COVID-19 Severity[a]	Anticoagulation at Discharge	Method of Assessment	Follow-up Time	Thromboembolism
Engelen, 2021 Belgium	ICU admission: 39%	28%	Follow-up clinic with DVT screen (ultrasound); further testing if high-risk	42 days post-discharge	DVT: 1% (1/146) PE: 1% (1/146)
Rashidi, 2020[92] Iran	ICU admission: 8%	NR	Telephone follow-up with in-person evaluation of patients reporting symptoms and documentation from patients already evaluated	45-55 days post-discharge	PE: 0.2% (3/1,529)
Alharthy, 2020[75] Saudi Arabia	ICU admission: 100%; "Severe" COVID-19	NR	All surviving patients assessed at 2 and 4 months; 49% were symptomatic at 4 months	60 days 120 days	DVT: 60 days: 14.2% (18/127) 120 days: 7.1% (9/127)
Daugherty, 2021[110] US	ICU admission: 13%	NR	Medical records	120 days post infection (mean)	DVT: COVID-19: 2.3% Control: 0.3% PE: COVID-19: 1.3% Control: 0.1%
Remy-Jardin, 2021[126] France	ICU admission: 42%	NR	Patients with residual respiratory symptoms and/or chest x-ray abnormalities who had dual-energy CT exam	144 days post-discharge (median)	PE: 2% (1/55)
Al-Aly, 2021[104] US (Veterans)	ICU admission: 26%	NR	Medical records	150 days post-discharge (median)	PE: Excess burden per 1000 COVID-persons vs seasonal influenza control group 18.31 (95%CI 15.8, 20.3) Thromboembolism: HR vs seasonal influenza group 2.3 (95%CI 1.9, 2.6)
Huang C, 2021[85] China	ICU admission: 4%	NR	21% randomly selected for US and CT post-discharge; 76% of those selected were evaluated	153 days post-discharge (median)	DVT or lower limbs (US): 0% (NOTE: post-discharge PE was an exclusion criteria [n=1])

Abbreviations: ICU=intensive care unit; NR=not reported; OR=odds ratio; VTE=venous thromboembolism

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]DVT, PE, limb ischemia due to coronary thrombosis, acute stroke, rapidly evolving hemodynamic instability with elevated D-dimer at time of presentation
[c]Subgroup of patients discharged without an indication for therapeutic anticoagulation and followed for 42 days although 5 (3%) received 7 days of standard dose low molecular weight heparin after a change in local COVID-19 guidelines
[d]Number discharged alive not reported

Bleeding Events

Three studies, none with control groups, reported bleeding events.[65,93,113] In a study from the US, at a median of 27 days post-discharge, 3.7% (6/163) experienced hemorrhagic events.[65] Two were considered 'major bleeds'; both followed falls. Four were considered 'clinically relevant non-major bleeding'. The patients experiencing thrombotic or hemorrhagic events had been discharged without anticoagulant therapy; among 13 patients discharged on thromboprophylaxis, there were no observed thrombotic or hemorrhagic complications. A study from Belgium reported no bleeding events at 6 weeks post-discharge regardless of thromboprophylaxis status[113] and a study from the UK reported no bleeding events at 6 weeks in the subgroup of patients discharged without an indication for therapeutic anticoagulation.[93]

Coagulation Disorders

Studies with Control Groups

Three database studies reported coagulations disorders.[104,109,110] The study of over 27,000 US Veterans reported an excess burden per 1000 COVID-19 persons at 6 months following COVID-19 infection of 14.3 (95%CI 10.1, 17.9) compared to a seasonal influenza control group.[104] Another US study, with data from over 36,000 individuals, reported a higher risk of hypercoagulability in the COVID-19 group (3.2%) than in a non-COVID control group (0.4%) during the 4 months after acute illness.[110] The risk difference was 2.8 (95%CI 2.3, 3.6) (P<.001). The third study, also from the US and including data from over 54,000 individuals, reported odds ratios (COVID-19 vs hospitalized non-COVID-19 patients) for coagulation and hemorrhagic disorders.[109] The ORs at 30, 60, 90, and 120 days were 1.3 (95%CI 1.0, 1.6), 1.3 (95%CI 0.95, 1.7), 0.65 (95%CI 0.5, 0.9), and 0.66 (95%CI 0.5, 0.97), respectively.

HEALTHCARE/RESOURCE UTILIZATION OUTCOMES

Key Findings

Frequently reported outcomes included discharge to a location other than home (3% to 47%, k=15) and all-cause hospital readmission (0% to 15%; k=20); 2-14% were readmitted within 30 days of discharge (k=11) and 0-15% at greater than 30 days (k=9). COVID-19-related readmissions were reported in 4-10% at follow-up periods of 5 to 90 days.

Few studies reported post-discharge oxygen or follow-up healthcare requirements.

Overview of Studies

Forty-seven studies – 25 from the US, 8 from Europe, 6 from the UK, 3 from China, 2 from Iran, and 1 each from the Democratic Republic of the Congo, Japan, and multiple nations – reported measures of healthcare and/or resource utilization (Appendix C, Tables 1 and 10).[26,28,31,32,37,38,40-

[44,47,50-52,54,56,58,59,64,65,67,69-72,76-78,80-83,85-87,89,90,112,127,128,136-138,142,143,146] Sample sizes ranged from 7 to 15,111 with 16 studies enrolling more than 1000 and 10 studies enrolling 100 or fewer. Mean or median ages ranged from 35 to 82. Between 0% and 94% were male. Race was reported in 28 studies with 5% to 90% White, 0% to 90% Black, 4% to 46% Hispanic, and 0% to 15% Asian. Diabetes was the most frequently reported comorbidity (42 studies), present in 2% to 71% of the study populations. COVID-19 severity was reported in 10 studies with 19% to 100% severe or critical. Between 1% and 100% were treated in the ICU (37 studies).

Discharge Disposition

Twenty-four studies reported on discharge disposition.[26,28,31,32,37,38,40-44,47,50-52,54,67,71,80,87,136-138,146] One included a control group.[28] As noted in the Methods, for the September 2021 version of the report we focused on post-discharge outcomes and therefore the findings from the June 2021 remain unchanged.

Five studies enrolled patients with stroke or neurological conditions and 4 enrolled other, specific populations are described below. Findings from the remaining studies are reported in Table 12. Studies reporting discharge other than to home are depicted in Figure 9.

Figure 9. Discharge Other Than Home

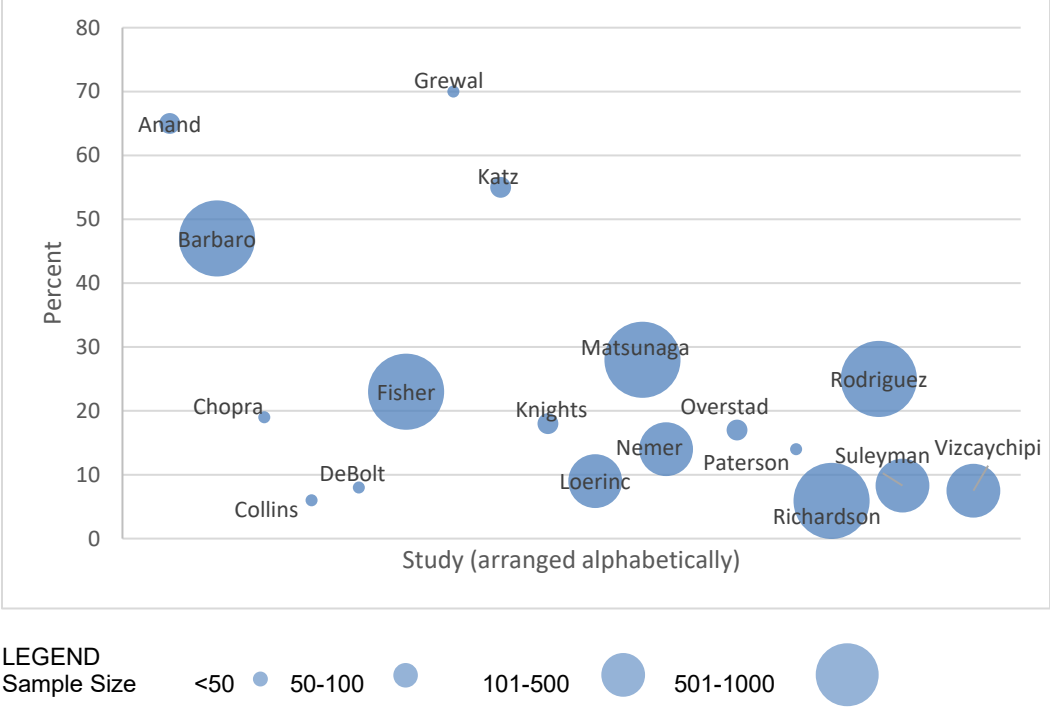


Table 12. Discharge Disposition (Author, Year in bold indicates study with comparator group)

Author, Year Country	COVID-19 Severity[a]	Home	Other Disposition
Atalla, 2020[136] USA	ICU admission: 33%	74% (14/19)[b] Home: 11; Hotel for Homeless with COVID-19: 3	Skilled nursing facility: 26% (5/19)[b]
Barbaro, 2020[41] Multi-national	ECMO support: 100%	Home or acute rehabilitation center: 53% (311/588)	Long-term acute care center or unspecified: 17% (101/588) Another hospital: 30% (176/588)
Chopra, 2020[80] USA	ICU admission: 13%	81% (13/16)	Nursing facility (permanent residence): 6% (1/16) Hotel for those with confirmed COVID-19: 13% (2/16)
Fisher, 2020[28] USA	ICU admission: 13%	77% (1,650/2,142) COVID-19 negative control group: 83% (788/950)	Nursing home: 23% (492/2142) COVID-19 negative control group: 17% (162/950)
Knights, 2020[137] United Kingdom	Invasive mechanical ventilation: 8%	81% (56/69)	Care home: 14% (10/69) Other not specified: 5% (3/69)
Loerinc, 2020[87] USA	ICU admission: 22%	91% (281/310)	Skilled nursing facility: 8% (25/310) Public health quarantine facility: 1% (4/310)
Matsunaga, 2020[47] Japan	32% severe	72% (1,762/2,437)	Long-term care facility: 2% (44/2,437) Another hospital: 18% (437/2,437) Non-medical (isolation) facility: 8% (194/2,437)
Nachega, 2020[50] Democratic Republic of the Congo	25% severe or critical	97% (645/665)	Home care: 3% (20/665)
Nemer, 2021[51] USA	ICU admission: 14%	85% (278/328)	Subacute facility: 12% (40/328) Hospice: 2% (8/328)
Overstad, 2020[52] Norway	19% critically ill	83% (52/63) ICU patients: 63% (5/8) Ward patients: 89% (49/55)	24-hour care: 17% (11/63) ICU patients: 38% (3/8) Ward patients: 13% (7/55)
Richardson, 2020[67] USA	ICU admission: 4%	94% (1,959/2,081)	Facility (*eg,* nursing home, rehabilitation): 6% (122/2,081)
Rodriguez, 2020[54] USA	ICU admission: 29%	74% (4,746/6,421)	Nursing facility: 17% (1,097/6,421) Another hospital: 5% (317/6,421) Hospice: 3% (192/6,421)
Suleyman, 2020[138] USA	ICU admission: 40%	92% (232/253) ICU patients: 79% (49/62) General practice unit: 96% (183/191)	Rehabilitation center: 8% (21/253) ICU patients: 21% (13/62) General practice unit: 4% (8/191)

Author, Year Country	COVID-19 Severity[a]	Home	Other Disposition
Vizcaychipi, 2020[38] United Kingdom	ICU admission: 14%	92.5% (614/664)	Temporary home: 2% (16/664) Residential care home: 5% (34/664)
Wang, 2020[71] China	53% severe	87% (114/131)	Community quarantine: 9% (12/131) Designated hospital: 4% (5/131)

Abbreviation: ECMO=extracorporeal membrane oxygenation
[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]Discharge disposition for 19 patients readmitted at a median of 5 days post-discharge
[c]Pregnant women admitted to hospital for COVID-19

Patients with Stroke or Neurological Conditions

Five studies enrolled patients with stroke or other neurological conditions.[31,32,37,40,146] Four studies were from the US.

Studies with Control Groups

A US study of stroke patients (some had stroke onset during COVID-19 hospitalization and some had COVID-19 onset within 14 days of stroke onset) reported that 45% (25/56 discharged) were discharged home and 55% (31/56) to rehabilitation.[32] An additional 30 patients had died or were in hospice care (data not reported separately for deaths and hospice). In a comparison group of non-COVID-19 stroke patients, 52% (228/438 discharged) were discharged home and 48% (210/438) to rehabilitation. An additional 61 patients had died or were in hospice care.[32]

Another US study of patients with ICD-10 codes at discharge for ischemic stroke and COVID-19 reported a favorable discharge (home or acute rehabilitation) for 34% (707/2086).[146] The same outcome was reported for 66% (110,546/166,586) of a historical control group.

Studies without Control Groups

One US study of patients who experienced a stroke reported that 30% (3/10) were discharged home (including 2 of 6 hospitalized for COVID-19 who subsequently experienced a stroke ['COVID'] and 1 of 4 hospitalized for stroke symptoms who subsequently tested positive for COVID-19 ['Neuro']), 50% (5/10) were discharged to acute rehabilitation (3 of 6 in 'COVID' group, 2 of 4 in 'Neuro' group), and 20% (2/10) were discharged to long-term acute care (1 of 6 in "COVID' group and 1 of 4 in 'Neuro' group).[31] Another US study enrolled patients who received a neurologic or neurocritical care admission or consultation.[40] Of the 64 patients discharged, 34% (22/64) went home without services, 32% (20/64) went to a skilled nursing facility, 14% (9/64) went to acute rehabilitation, 8% (5/64) when home with services, 6% (4/64) were in inpatient hospice, 5% (3/64) were in a long-term acute care hospital, and 2% (1/64) was home with hospice. A study from the United Kingdom, reported that, of COVID-19 neurological patients discharged, 56% (9/16) went home and 31% (5/16) went to a rehabilitation or stroke unit; the location of 13% (2/16) was not reported.[37]

Other Populations

Studies with Control Groups

A US study of pregnant women admitted for severe or critical COVID-19 reported that 92% (35/38) were discharged home without oxygen required and 8% (3/38) were discharged to either a skilled nursing facility, long-term acute care, or home with oxygen required.[43] In a comparison group of non-pregnant women with severe or critical COVID-19, 85% (77/91) were discharged home without oxygen required and 15% (14/91 to another facility or home with oxygen required.

Another US study enrolled patients with a history of heart failure.[42] Among patients with COVID-19, 7% (428/6,357) were discharge to hospice and 41% (2,605/6,357) to skilled nursing or rehabilitative care. In a comparison group of non-COVID patients, 4% (4,068/95,556) were discharged to hospice and 21% (20,352/95,556) to skilled nursing or rehabilitative care.

Studies without Control Groups

One US study enrolled 20 patients with HIV who were hospitalized for COVID-19; 4 patients (20%) were from a VA Medical Center.[26] Of patients discharged, 81% (13/16) were discharged home, 6% (1/16) to a nursing facility (permanent residence), and 13% (2/16) to a hotel for those with confirmed COVID-19. Five of the 20 patients enrolled had been living in a group living situation prior to hospitalization (3 in nursing homes, 1 incarcerated, and 1 in a substance abuse recovery home).

Patients with COVID-19 and Takotsubu cardiomyopathy were included in a study from the US.[44] Three of 7 patients were discharged alive, 1 (33%) to a skilled nursing facility, and 2 (67%) to long-term acute care.

Hospital Readmission

Hospital readmission for any reason was reported by 22 studies.[56,58,59,64,65,67,69-71,77,78,80,83,86,87,89,90,136-138,142,143] For the current version of the report, we focused only on readmission related to COVID-19 and identified 3 additional studies.[112,127,128]

One study from the US enrolled individuals who were hospitalized for a hip fracture and tested positive for COVID-19 either before, during, or after (*ie,* during rehabilitation) hospitalization.[58] Twenty-nine percent had been admitted to the ICU. Within 30 days of follow-up, 12% (2/17) of the COVID-19 confirmed positive patients, 7% (1/14) of the COVID-19 suspected positive patients, and 3% (3/107) of the COVID-19 confirmed negative patients were readmitted.

The remaining studies are summarized in Table 13. One study included a control group.[78]

Table 13. Hospital Readmission (shaded rows indicate studies added for September 2021 update; Author, Year in bold indicates study with comparator group)

Author, Year Country	COVID-19 Severity[a]	Length of Follow-up	Readmission
Richardson, 2020[67] USA	ICU admission: 4%	3 days (median to readmission)	2% (45/2,081)

Author, Year Country	COVID-19 Severity[a]	Length of Follow-up	Readmission
Atalla, 2020[136] USA	ICU admission: 33%	5 days (median to readmission)	6% (19/339) (15 likely COVID-19 related)
Parra, 2020[90] Spain	ICU admission: 5%	6 days (median to readmission)	4% (61/1,368)
Wang, 2020[71] China	23% severe	7-14 days	4% (5/131)
Somani, 2020[70] USA	ICU admission: 19%	14 days	2% (56/2,864)
Brendish, 2020[78] United Kingdom	ICU admission: 10%	30 days	11% (30/352) COVID-19 negative control group: 18% (105/702)
Hamilton, 2020[83] United Kingdom	ICU admission: 16%	30 days	8% (86/1,032)
Loerinc, 2020[87] USA	ICU admission: 22%	30 days	5% (16/310) (69% [11/16] attributed to COVID-19)
Monday, 2020[89] USA(Veterans)	ICU admission: 34%	30 days (from admission)	14% (8/57)
Patell, 2020[65] USA	ICU admission: 26%	30 days	7% (12/163)
Suleyman, 2020[138] USA	ICU admission: 40%	30 days	11% (29/253) ICU: 3% (2/62) General practice unit: 14% (27/191)
Bowles, 2020[77] USA	NR	32 days (mean)	10% (137/1,409) while in home health care
Knights, 2020[137] United Kingdom	Invasive mechanical ventilation: 8%	36 days (median) (from admission)	5% (3/56)
Casas-Rojo, 2020[56] Spain	ICU admission: 8%	40 days (median)	5% (573/11,928)
De Michieli, 2021[112] USA	ICU admission: 28%	49 days (median)	10% (30/312) COVID-19 related
Chopra, 2020[80] USA	ICU admission: 13%	60 days	15% (189/1,250)
Spinicci, 2021[127] Italy	12% severe, 47% critical	60 days (median)	10% (10/100) COVID-19 related (5 for cardiac disease, 2 for infectious disease, 2 for neurologic disorders, 1 for respiratory symptoms)
Khalili, 2020[86] Iran	Invasive mechanical ventilation: 11%	90 days (from initial admission)	4% (10/254)
Nersesjan, 2021[142] Denmark	ICU admission: 47%	90 days	38% (17/45)[b]
Suarez-Robles, 2021[128] France	ICU admission: 1%	90 days	5% (7/134) for bacterial respiratory infection, pulmonary thromboembolism, exacerbated COPD
Dawson, 2020[143] United Kingdom	ICU admission: 49%	NR	0% (0/208)

Author, Year Country	COVID-19 Severity[a]	Length of Follow-up	Readmission
El Moheb, 2020[59] USA	ICU admission: 100% (inclusion criteria)	NR	11% (10/92) Matched COVID-19 negative:11% (10/92)
Lovinsky-Desir, 2020[64] USA	Invasive mechanical ventilation: 21%	NR	5% (40/832) in 40-65 age group without asthma 5% (5/111) in 40-65 age group with asthma
Sachdeva, 2020[69] USA	ICU admission: 27%	NR	9% (1/9)

[a]Severity (%) as defined by study authors; if severity not reported, maximum oxygen requirements or ICU admission used as markers of severity
[b]Patients were discharged to a tertiary referral center following hospitalization

Post-discharge Treatment

Oxygen Therapy

Use of oxygen therapy was reported in 9 studies. A US study of Veterans reported home oxygen was required in 39% (22/57).[89] Follow-up was 30 days. New home oxygen therapy was required for 13% (41/310) of patients in another US study (30 day follow-up).[87] A third US study reported 7% (32/488) required oxygen at home and 7% (34/488) required new use of CPAP or other assistance when sleeping.[80] Follow-up was 60 days.

A study from China reported that 6% (5/85) were receiving oxygen therapy via nasal cannula at home (time post-discharge not specified).[72] Wang et al, also from China, reported that at 1-2 weeks after discharge 7% (9/131) were treated with oxygen therapy.[71] At 3-4 weeks, the percentage decreased to 1% (1/131). Corticosteroid use was 4% (5/131) at 1-2 weeks and 2% (2/131) at 3-4 weeks. A study from Japan reported that 8% (182/2,430) required oxygen therapy at discharge.[47] A study from Germany reported that 82% (27/33) of patients required oxygen therapy at admission; at 6 week follow-up, only 1 patient required oxygen therapy.[81] Two additional studies from Europe reported oxygen therapy at 2 months for 5% (5/100)[127] and at 3 months for 3%.[128]

Post-acute Care

A US study reported need for post-acute rehabilitation in patients undergoing surgery for hip fracture.[58] Ninety percent (9/17) of the COVID-19 group was receiving rehabilitation compared with 78.3% (83/107) of patients negative for COVID-19. The difference was not statistically significant (P=.61). Another US study reported the need for physical or occupational therapy in 14% (42/310) and home nursing service in 5% (16/310).[87] Follow-up in both studies was 30 days.

Several studies reported on self-care ability post-discharge. In a study from Iran, where 18% of patients were admitted to the ICU, 88% (370/420) reported no problems with self-care at a mean of 22 days post-discharge.[76] A study from China reported that 1% (11/1,622) had personal care problems; median follow-up was 153 days.[85] Among patients from a study in Japan, 32% with severe COVID-19, 84% (2,045/2,4245) rated their self-care ability at the time of discharge the

same as before COVID-19, 10% (237/2,425) rated it worsened, and 4% (106/2,425) rated it improved.[47]

Follow-up health care was also reported in several studies. "Need for follow-up" was reported for 60% (75/126) of patients enrolled in a study from Italy.[82] Need was determined based on elevated respiratory rate, uncontrolled blood pressure, moderate to very severe dyspnea, malnutrition, or new onset cognitive impairment. Recommended follow-up care was identified in a study from the US.[87] Primary care appointments were recommended for 83% (258/310) and specialist appointments (including nephrology and cardiology) for 28% (90/310). Follow-up bloodwork was ordered for 10% (31/310) and follow-up radiology for 7% (21/310). A study from the US reported primary care follow-up within 60 days of discharge for 78% (382/488) of patients who completed a follow-up telephone survey.[80] Total enrollment was 1,250. As with most other outcomes, the lack of controls hospitalized without COVID-19 limits conclusions.

A study from the US reported new short-term medications were required by 67% (207/310) of patients with an average of 2.2 new prescriptions per patient.[87] New long-term medications were required for 23% (72/310) with an average of 1.6 new prescriptions per patient.

In a study from the United Kingdom, new "packages of care" were required for 2.9% (2/69) of patients discharged and an increase in mobility aids was noted for 11.6% (8/69).[137]

DISCUSSION

Our review identified 124 reports of post-acute major organ damage or healthcare/service use outcomes in patients who were hospitalized with or for COVID-19. Thirty-three studies were from the US including 2 studies exclusively of Veterans and 1 multisite US study that included patients from a VA Medical Center. The amount of data is increasing rapidly. We provide "Key Findings", "Limitations", and "Suggestions for Future Research".

KEY FINDINGS

Key Question 1

Recent evidence includes 4 large database studies, 2 from the US including 1 study of US Veterans, identifying post-hospitalization, incident respiratory, cardiac, neuromuscular, endocrine, renal, gastrointestinal, and hematologic disease in COVID-19 and control groups. However, the majority of studies enroll convenience samples without controls, providing wide-ranging prevalence estimates based mainly on physiologic data. Outcomes associated with COVID-19 variants are unknown.

Available evidence suggests:

- In studies with control groups, incident respiratory disease may be higher in post-hospitalization COVID-19 cases (k=3). Prevalences ranged from 2% to 22% in COVID-19 groups compared to less than 1% in control groups. Dyspnea was more prevalent (64% vs 10%) or Veterans were at greater risk for dyspnea (HR 1.14 [95%CI 1.04, 1.26]) in COVID-19 groups than in control groups. Other reported pulmonary outcomes included radiographically defined fibrosis at varying time intervals (k=12, none with

control groups) with estimates ranging from 0% to 61% of enrolled patients, abnormal diffusing capacity of the lung for carbon monoxide (DLCO) in 16% to 57% (k=15, none with control groups), and dyspnea present at >1 month post-discharge in 2 to 81% (k=26, including 2 with control groups noted above). Interpretation of the findings is limited by varying degrees of COVID-19 severity and different outcome definitions, assessment methods, sampling strategies, and follow-up lengths.

- In studies with control groups, patients with COVID-19 were at greater risk for post-discharge incident cardiovascular disease outcomes (including acute myocardial infraction, coronary disease, heart failure) compared to controls. Prevalences of new cardiovascular events ranged from approximately 1 to 3% of the COVID-19 groups and less than 1% in the control groups (k=3). Myocardial inflammation/fibrosis was more prevalent in COVID-19 patients than controls (k=3). Pericardial effusion was reported in 0% to 20% (k=6). Impairment in left ventricular ejection fraction (LVEF) was noted in 0-22% (k=8).

- The prevalence, or risk for, stroke was higher in COVID-19 groups than in matched control groups (k=2). The incidence of dementia or Alzheimer's post-COVID-19 was low but may exceed that of non-COVID cases. In 5 studies using established cognitive function assessment tools with specified thresholds, cognitive impairment was observed in 23% to 57%. One of the studies included a community-based control group and reported no statistically significant difference between the COVID-19 and control groups. Cognitive symptoms including attention deficits, confusion, and memory difficulty were reported in 5% to 34% of COVID-19 patients (k=9). Findings are limited by lack of assessment of cognition prior to hospitalization for COVID-19. A "good" prognosis based on modified Rankin Scale scores at the time of discharge was reported in 17% to 60% of patients hospitalized for stroke and testing positive for COVID-19 (k=6).

- The prevalence of, or risk for, new onset chronic kidney disease and acute kidney injury following hospitalization for COVID-19 was greater than in matched control groups (k=4). Need for renal replacement therapy (RRT) at discharge was reported in 4% to 34% of those who had required RRT during hospitalization (k=5).

- Three large database studies, 1 from the US enrolling Veterans, reported greater risk of new onset diabetes following hospitalization for COVID-19 compared to matched control groups consisting of individuals either hospitalized for seasonal influenza, from the general population, or without COVID-19.

- Large database studies identified an excess burden of incident gastrointestinal disorders in individuals hospitalized for COVID-19 compared to seasonal influenza and a higher incidence of new onset chronic liver disease in individuals hospitalized for COVID-19 compared to non-COVID controls.

- Post-discharge VTE was reported in 0% to 14% (k=17). Bleeding events were rare. The prevalence of, or risk for, coagulation disorders was higher in COVID-19 groups than in control groups. Interpretation is limited by varying time points post-discharge (5 days to 153 days), little reporting on prophylactic anticoagulant use, and varying study inclusion

criteria (*ie,* assessment of individuals with versus without signs or symptoms of VTE; follow-up of all patients via medical records, outpatient clinics, or telephone contact vs evaluation of patients with suspicion of VTE).

Key Question 2

We are unable to determine if post-acute care prevalence of major organ damage varies by patient characteristics (*eg,* age, sex, race/ethnicity, pre-existing comorbidities/frailty, type of residence), COVID-19 disease severity, or other factors (*eg,* vaccine status, treatment for COVID-19). Few studies reported outcomes for subgroups of patients.

Key Question 3

Frequently reported outcomes included discharge to a location other than home (3% to 47%, k=15) and all-cause hospital readmission (0% to 15%; k=20); 2-14% were readmitted within 30 days of discharge (k=11) and 0-15% at greater than 30 days (k=9). COVID-19 related readmissions were reported in 4-10% at follow-up periods of 5 to 90 days. Few studies reported post-discharge oxygen or follow-up health care requirements including post-hospital need for ambulatory care, imaging or laboratory monitoring needed, or treatments (*ie,* medications, devices, procedures, surgery) required.

LIMITATIONS

Additional limitations of the available evidence include:

- Although recent evidence includes 4 database studies with control groups, most available data are from studies of small, convenience samples (often from a single hospital site) with poorly described study populations or measures of major organ damage.
- Most studies were not conducted in the US and only 2, one reporting major organ damage and the other reporting readmission and need for home oxygen, enrolled exclusively Veterans.
- 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.
- Many studies assessed outcomes at discharge or had short follow-up post-discharge; long-term major organ damage prevalence and healthcare/service use needs are unknown.
- There are no data reporting on outcomes based on patient living situation prior to COVID-19 infection (*ie*, community dwelling versus nursing home or assisted care centers)
- No data exist to ascertain if outcomes differ based on COVID-19 vaccination status or with infection with different COVID-19 variants.

Limitations of our review methods include:

- We defined "post-acute COVID" as patients being post-hospital discharge. The applicability of these findings to non-hospitalized patients with acute COVID symptoms is unknown; this was out of our scope.

- Our literature search was through May 2021 and would not have included information published after that date.

FUTURE RESEARCH

Given the gaps in, and limitations of, the existing evidence,[148] the following may serve as a guide for future research to better inform healthcare systems as they plan for on-going care of patients recovering from COVID-19.[149]

Population

We chose to define "post-acute" as post-hospitalization but other definitions may be appropriate.[3,148] For example, patients with acute COVID-19 who are not hospitalized may have "post-acute" major organ damage. Limiting the scope of this review to patients hospitalized for acute COVID likely underestimates the total burden of post-acute major organ damage. This should be acknowledged for resource allocation planning in the future. Furthermore, we did not identify studies that assessed "long-haulers" or "long COVID" (*ie,* people who have either recovered from COVID-19 but still report lasting effects or who have had the usual symptoms for longer than might be expected).[150] This is a poorly defined entity and no published data were available. Additionally, there are likely important difference in patients hospitalized *for* COVID-19 versus patients hospitalized for another indication who have a positive COVID-19 test. We chose to include both, since given the protean manifestations of COVID-19 illness, it is often hard to clinically differentiate the two, but this could influence prevalence, severity, and causality of findings. We also limited eligibility to studies that assessed patients with "confirmed" COVID-19. While this increases the specificity and accuracy of our review it likely underestimates the magnitude of burden of post-acute.

Future studies should include all patients or consecutive patients rather than convenience samples. Study populations should be carefully described including severity of disease and treatments received. Results should be reported for subgroups based on age, gender, race/ethnicity, pre-existing conditions/frailty, vaccine status, type of residence (*eg,* independent living, assisted living, nursing home), COVID-19 severity, COVID-19 variant, and treatment received. Ideally, researchers would be able to link pre-COVID-19 data with post-COVID-19 data. Without pre- and post- data, it is difficult to isolate the effects of COVID-19.

Comparator

The use of matched non-COVID-19 control groups, ideally hospitalized for a non-COVID-19 respiratory illness such as influenza or RSV, would allow for a better understanding of the effects of COVID-19. Without appropriate comparators and information on pre-COVID comorbidities it is not possible to accurately determine the effect that COVID-19 has on post-discharge health outcomes. Nonetheless, given ongoing health and healthcare concerns associated with COVID-19, uncontrolled reports among patients with COVID-19 are still informative for care planning.

Outcomes

Many studies, excluded from our review, reported mean and median values of laboratory, radiologic, or physiologic measures. These data do not provide prevalence outcomes. Future research should include measures that will reflect prevalence of major organ damage or disease based on accepted definitions of disease, even if defined as asymptomatic laboratory, radiologic, or physiologic measures. Although many conditions have been reported to be associated with COVID-19 while patients are hospitalized, there has been little or no published post-hospital data for most of those conditions. Many reports were convenience samples and used testing measures available at that facility or selected for reporting for unclear reasons. Criteria for outcome assessment, reporting and definition will have important implications on major organ damage prevalence and severity.

Timing

Future research would ideally link pre-COVID-19 patient comorbidities to status at discharge and include standardized and longer follow-up to identify persistence of COVID-related conditions.

Setting

Information on major organ damage prevalence and healthcare/service use needs of non-hospitalized patients is also needed.

ONGOING DATA COLLECTION

We are aware of several ongoing studies:

- A study of COVID-19 sequelae among Veterans treated in the VA (https://www.hsrd.research.va.gov/research/abstracts.cfm?Project_ID=2141707422),
- A natural history study of COVID-19 titled "Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential" (EPICC-EID); a collaboration between the VA and the Department of Defense to better understand the clinical course of COVID-19 (https://www.research.va.gov/covid-19.cfm),
- A study sponsored by UK-based Perspectum Diagnostics (https://www.bioworld.com/articles/434620-perspectum-launches-study-of-post-covid-19-organ-damage),
- The Post-hospital COVID (PHOSP-COVID) study,[150]
- A multicenter observational registry, the North American COVID-19 ST-Segment-Elevation Myocardial Infarction (NACMI) registry, to collect data on ST elevation in COVID-19 patients to determine the etiology and associated clinical outcomes,[151]
- An initiative from the NIH: Post-Acute Sequelae of SARS-CoV-2 infection (PASC) (NIH launches new initiative to study "Long COVID" | National Institutes of Health (NIH)).

- The Johns Hopkins COVID Long Study (Johns Hopkins COVID Long Study (covid-long.com).

- The Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study (https://www.cuimc.columbia.edu/news/nationwide-study-covid-19-risk-and-long-term-effects-underway-37-academic-medical-centers); a nationwide study of more than 50,000 individuals jointly funded by the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging of the National Institutes of Health (design paper: https://www.medrxiv.org/content/10.1101/2021.03.19.21253986v1.full.pdf)

Several major healthcare systems have established multidisciplinary post-COVID care clinics including the Mount Sinai (New York) Center for Post-COVID Care, the Penn Medicine Post-COVID Recovery Clinic, University of California San Francisco's OPTIMAL Clinic, the University of Michigan's Post ICU Longitudinal Survivor Experience (PULSE) Clinic (now focused on post-COVID-19), the Columbia University Irving Medical Center COVID-19 Rehabilitation Program, and the Mayo Clinic COVID Activity Rehabilitation Program (CARP). Anticipated post-acute care rehabilitation needs of patients and guidance on how to address those needs have been reported.[152-161] There is an emphasis on multi-disciplinary programs to address respiratory, cardiovascular, thromboembolism, and neurological sequelae along with physical function and mental health needs. Patient groups have also been organized with a focus on long-term symptoms. These include Survivor Corps (https://www.survivorcorps.com/) and the COVID-19 "Long Hauler" Symptoms Survey,[16] the Body Politic COVID-19 support group (https://www.wearebodypolitic.com/covid19), Long Covid SOS in the UK (www.longcovidsos.org), and the COVID Symptom Study with an app to study symptoms and track the spread of the virus (https://covid.joinzoe.com/us-2).

CONCLUSIONS

Our systematic review on post-acute COVID-19 major organ damage and healthcare/service use needs found that most studies were from outside the United States and only 2 enrolled exclusively Veterans. There was little information on patient-centered or clinical health outcomes; most data were based on laboratory or imaging tests. Data were largely from studies of convenience samples with poorly described study populations and lacked control groups or pre-COVID-19 data. However, recent evidence included 4 large database studies with COVID-19 and control groups. Evidence from these studies suggests that compared to non-COVID-19 controls, adults hospitalized for COVID-19 had higher post-hospitalization incident respiratory, cardiac, liver, chronic and acute kidney disease, stroke, diabetes, and coagulation disorders. There was little or no information about post-hospital care, monitoring, or treatments required. Future research should: 1) include clear descriptions of the patient populations and the timing of outcome assessment with respect to hospitalization, 2) link pre-COVID-19 data with post-COVID-19 data, and 3) assess outcomes that allow for determination of prevalence of major organ damage and healthcare/service use needs.

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In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

David Atkins, MD, MPH
Director, Health Services Research & Development

Joseph Francis, MD
Chief Improvement & Analytics Officer, Office of Performance Measurement

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