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

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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 is comprised of 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 and Cochrane Collaboration. 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 comprised 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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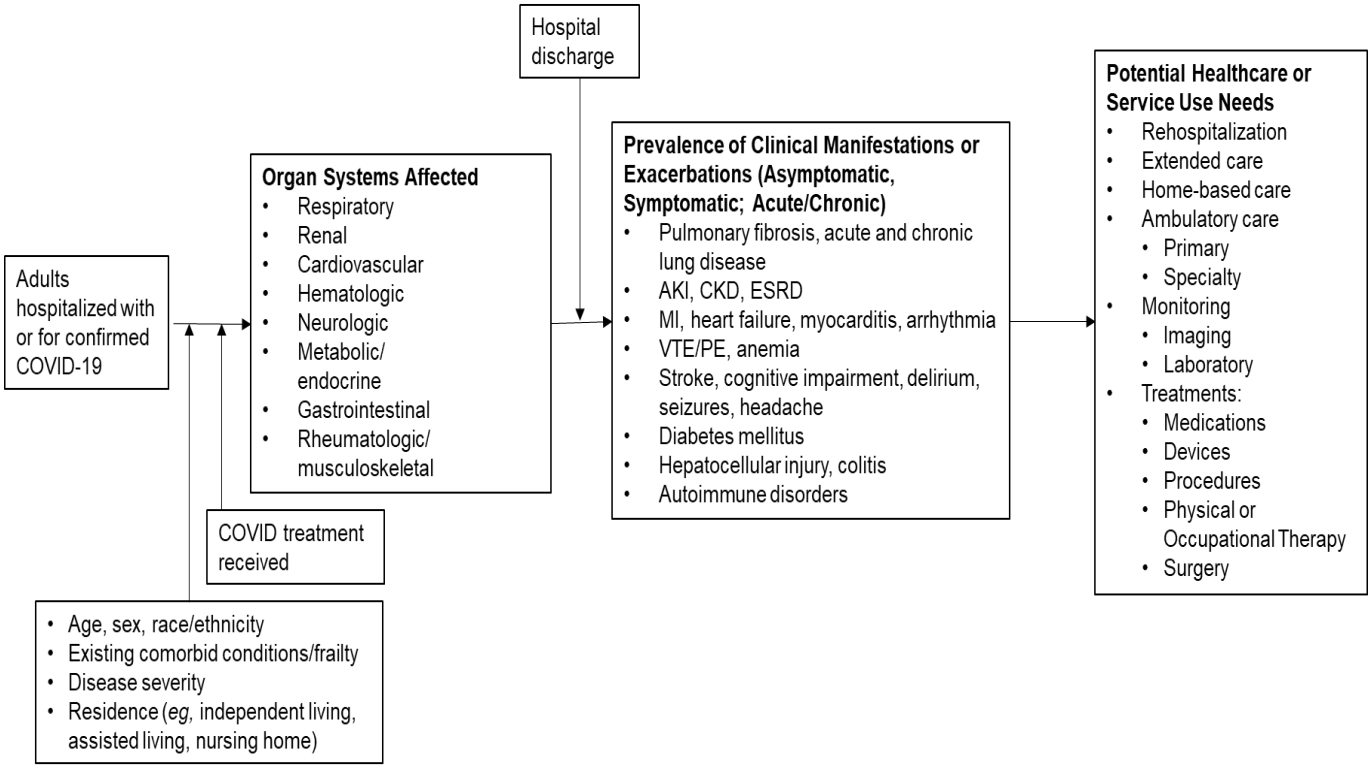
BACKGROUND

Coronavirus disease-2019 (COVID-19) is a viral illness that, as of December 1, 2020, was identified in over 62 million individuals (over 13 million in the US) in 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 1.4 million deaths worldwide (over 265,000 in the US) are attributed to 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] renal,[3,4] neurological,[5,6] hematologic,[7-9] endocrine,[10] and gastrointestinal.[11]

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 most common.[12-16] Multi-organ damage[17] and long-term clinical outcomes[18] 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.[19]

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. 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

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

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)?

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?

In consultation with VHA 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.

METHODS

Our protocol was registered in PROSPERO: CRD42020204788.

SEARCH STRATEGY

We searched MEDLINE, Embase, and the Cochrane Library from January 1, 2019 to October 6, 2020. 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 "preCOVID-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 contributing factor or identified incidentally on screening).

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. We assessed study quality characteristics using the Joanna Briggs Critical Appraisal Tool for case series[20] 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 outcomes data. We narratively synthesized the evidence.

Table 1. Study Eligibility Criteria

Study Characteristic	Include	Exclude
Population	Adults (age 18 and older)	Children or adolescents, age <18; MERS; SARS
Intervention	Discharge (or ready for discharge) from hospitalization after admission with or for proven COVID-19	Data 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	None
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	No outcomes of interest
Timing	Short-term (< 3 months) and long-term (≥ 3 months) post-discharge	None
Setting	Any post-discharge setting (*eg*, home, rehabilitation or long-term care facility); may include re-hospitalization	None
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

LIVING REVIEW

We plan to update our literature search, using the search strategy outlined above, at least every 3 months through December 2021 for new evidence related to post-acute major organ damage and associated healthcare/service use needs. Study eligibility criteria, procedures for data abstraction, and risk of bias assessment will remain the same. Our data synthesis plan may change if future evidence allows. New evidence that does not substantially change review conclusions will be summarized every 3 months. New evidence that changes review conclusions or certainty of evidence will be incorporated into a major update.

PEER REVIEW

A draft version of this report underwent peer review by content experts and clinical leadership. Reviewer comments and our responses are presented in Appendix B and the final report incorporates these comments.

RESULTS

KEY FINDINGS

Key Question 1: Limited post-hospital data with wide ranging prevalence estimates that mainly rely on physiologic outcomes from convenience samples without controls; most not conducted in US.

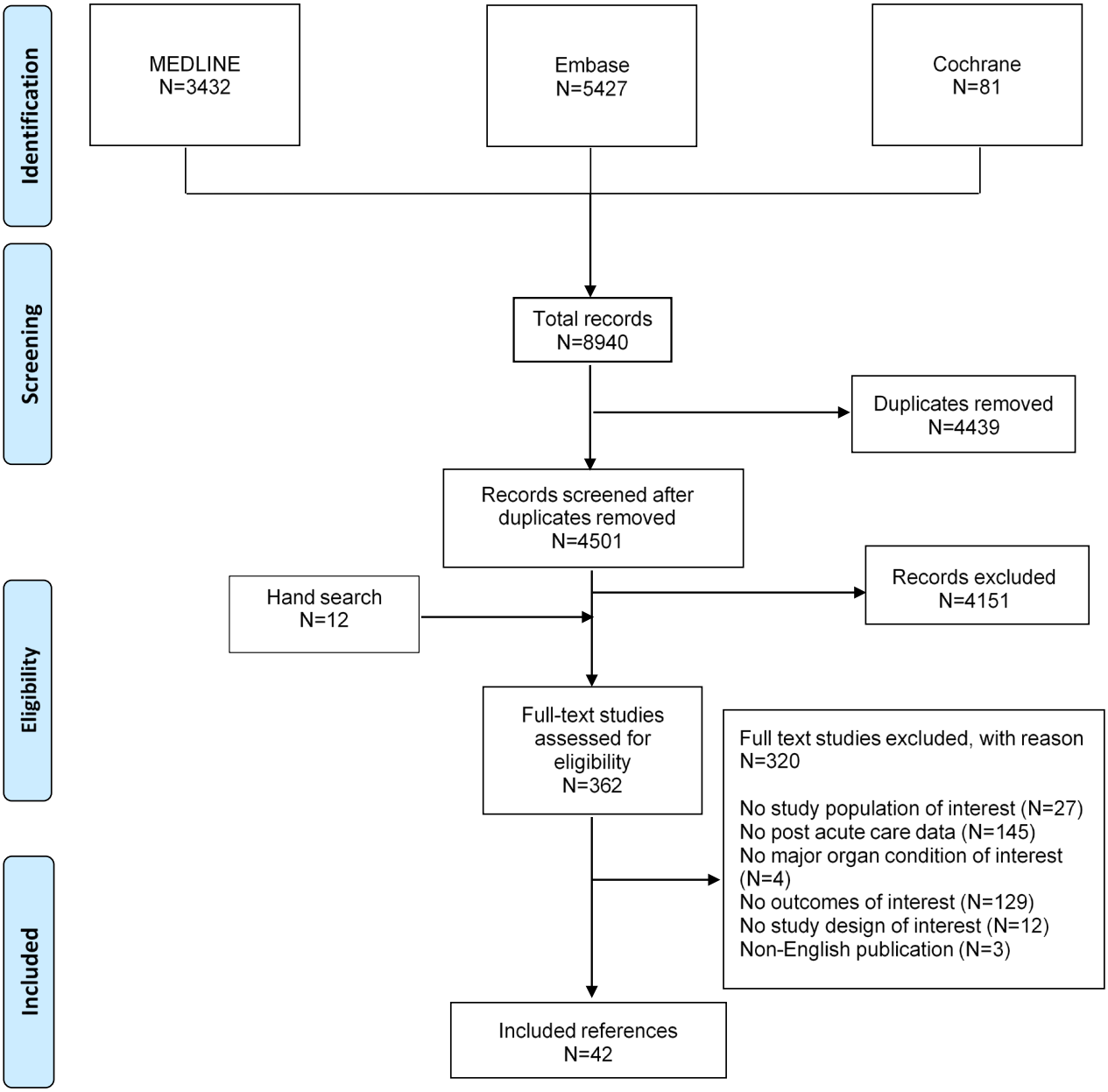
Key Question 2: Information is insufficient to assess if prevalence varies by patient, disease, and comorbidity factors.

Key Question 3: Little information on post-hospitalization resource use including discharge disposition and readmission.

PRISMA FLOW DIAGRAM

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

Figure 2. PRISMA Flow Diagram



OVERVIEW OF INCLUDED STUDIES

We identified 42 studies reporting outcomes data (Table 2) at the time of hospital discharge (k=17),[21-37] post-discharge (10 studies at 30 days or fewer follow-up) (k=22),[38-59] or both (k=3).[60-62]

Twelve studies reported pulmonary outcomes,[21,22,26,28,29,33,39,42,43,46,55,58,59] 6 reported neurological outcomes,[21,23,30,32,35,43] 4 studies reported cardiovascular outcomes,[22,39,45,49] 3 reported renal outcomes,[24,34,39] 3 reported hematologic outcomes,[22,48,51] 1 reported gastrointestinal outcomes,[39] and 22 reported healthcare or resource utilization outcomes.[25,27,30,31,36-38,40,41,44,47,48,50,52-57,60-62] Studies were typically described as retrospective, case series, or cross-sectional although 9 were described as prospective cohort studies.[21,22,37,39,40,43,49,51,55] We did not formally rate study risk of bias. Twenty-five of 42 studies enrolled all or consecutive patients, 18 were single-site studies, 18 provided little information about the group of patients discharged or the time of the follow-up with respect to the time of discharge, and many were unclear about data sources and completeness of follow-up. 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.

PULMONARY OUTCOMES

Of the 12 studies reporting pulmonary outcomes (Appendix C, Tables 1 and 3), 5 were from China,[33,46,55,58,59] 6 were from Europe,[26,28,29,39,42,43] and 1 was from the Middle East.[22] Sample sizes ranged from 18 to 131 with all but 5 studies enrolling 50 or fewer individuals. Mean or median ages ranged from 37 to 73 years and the percentage of males enrolled ranged from 35% to 84%. Seven studies reported hospital length of stay with mean or median values ranging from 10 to 28 days.[26,29,43,46,55,58,59] Eight studies reported ICU admission. One study excluded patients admitted to the ICU[33] and 2 enrolled only post-ICU patients.[22,26] In the other 5 studies, 3% to 31% were admitted to ICUs. One study excluded patients who received mechanical ventilation[33]; in the other 5 studies reporting, between 2% and 100% received mechanical ventilation. None of the studies included a comparison to non-COVID-19 patients. Reported outcomes varied across the studies with most reporting surrogate measures of health outcomes.

Table 2. Overview of Included Studies

Major "Organ" of Interest								
# Studies*	12	4	6	3	22	0	1	3
Location	China: 5 Europe: 6 Middle East: 1	China: 1 Europe: 2 Middle East: 1	Europe: 2 US: 2 Multiple: 2	US: 2 Europe: 1	China: 3 US: 13 Europe: 4	NA	Europe	US: 1 Europe: 1 Middle East: 1
Time of Assessment	Hospital DC: 4 Rehab Unit Admission: 1 Post-DC: 7	Hospital DC: 1 Post-DC: 3	Hospital DC: 5 Post DC: 1	Hospital DC: 2 Post DC: 1	Hospital DC: 6 Post-DC: 11 Hospital DC and post-DC: 5	NA	Post DC	Hospital DC: 1 Post DC: 2
Outcomes	Pulmonary fibrosis: 7 to 44%[46,58,59] Reduced Pulmonary function: 9 to 25%[33,46,58] Reduced DLCO:47 to 53%[33,42,46] Dyspnea: 100% (severe)[26]; 29% (mild to severe)[43] Other: PaO_2/FiO_2, respiratory support, impairment	Impaired EF: 11%[39] Pericardial effusion: 1.5% Ultrasound[22]; 20% CMR[49] LGE: 22 to 32%[45,49] Native T1, T2: elevated in COVID-19[45,49] Elevated hsTNT: 5%[49]	NIH Stroke scale: moderate symptoms[23,30] Modified Rankin Scale "moderate-to-severe" stroke sequelae: 29 to 83%[21,23,30,32,35]	AKD: 28 to 35%[24,34] Need for KRT: 31% survivors on KRT in hospital[34] Impairment imaging: 22%[39]	Positive SARS-CoV-2 (post DC): 9 to 63%[44,54,55,57,60] Readmission: 2 to 12%[38,40,41,47,48,50,52,53,55,60-62] Discharge: Home: 35 to 93%; Rehabilitation other care: 2 to 50%; Nursing home: 6 to 15%[25,27,30,31,36,37,50,55,60-62] Other: post-DC treatment	NA	Liver inflammation on imaging: 16%[39]	DVT: 12.5%[22] Thrombo-embolism: 0.5 to 2.5%[48,51] Hemorrhage: 3.7%[48]

AKD=acute kidney disease; CMR: cardiac magnetic resonance imaging; DC=discharge; DLCO=diffusing capacity for carbon dioxide; DVT=deep venous thrombosis; EF=ejection fraction; hsTNT=high-sensitivity Troponin; KRT=kidney replacement therapy; LGE=late gadolinium enhancement; MRI=magnetic resonance imaging; NA=not available (no studies reporting); US=United States

*Studies may appear in more than 1 column

Pulmonary; Cardiac; Neurologic; Renal; Resource Use; Musculoskeletal and Endocrine; Gastrointestinal; Hematologic

Radiographic Fibrosis

Three studies reported the percentage of patients with pulmonary fibrosis. One study defined fibrosis on CT chest imaging as a combination of findings including parenchymal bands, irregular interfaces, coarse reticular pattern, and traction bronchiectasis.[59] At a median of 8 days post-discharge, pulmonary fibrosis was identified in 44% (14/32).[59] The other 2 studies did not report how fibrosis was diagnosed. In 1 study, at 30 days post-discharge, 7% (4/57) had pulmonary fibrosis.[46] The other study, assessing outcomes at a mean of 38 days post-discharge, reported 22% (4/18) with pulmonary fibrosis and 61% (11/18) with ground-glass opacity plus pulmonary fibrosis.[58]

Pulmonary Function

Pulmonary function tests were also reported by 3 studies. The percentage of patients with forced expiratory volume in 1 second (FEV_1) less than 80% of predicted was 14% (15/110) in 1 study assessing lung volume at discharge[33] and 9% (5/57)[46] and 17% (3/18)[58] in 2 studies assessing lung volume at ≥30 days post-discharge. In the same studies, the percentage of patients with forced vital capacity (FVC) less than 80% of predicted was 9% (10/110) in the study assessing lung volume at discharge[33] and 11% (6/57)[46] and 17% (3/18)[58] in studies assessing lung volume at ≥30days. An FEV_1/FVC ratio of less than 80% at 30 days post-discharge was noted in 44% (25/57)[46] while a ratio of less than 70% was noted at discharge in 5% (5/110)[33] and at 38 days post-discharge in 17% (3/18).[58] For all 3 outcomes there were no significant differences between subgroups based on COVID-19 severity. Total lung capacity less than 80% of predicted was reported in 2 studies: 12% (7/57) in 1 study[46] and 25% (27/110) in the other.[33] Mo et al reported a significantly (P<.05) higher percentage of patients with TLC <80% predicted in the severe pneumonia subgroup (47%) than in the mild (17%) or pneumonia (21%) subgroups[33] while Huang et al reported no difference based on severity.[46]

Ventilation Impairment

Two studies, both assessing lung function at approximately 1 month post-discharge, characterized ventilation impairment as restrictive or obstructive. In 1 study, 11% (6/57) were characterized as having obstructive impairment, 12% (7/57) as restrictive impairment, and 4% (2/57) as combined obstructive and restrictive.[46] In the second study, 17% (3/18) had obstructive impairment and 17% (3/18) had restrictive impairment.[58] Another study, not yet peer-reviewed, measured lung impairment with MRI at a median of 105 days after a positive COVID-19 result.[39] Deep breathing fractional area change of <39% was observed in 47% (16/34) evaluated.

Diffusing Capacity

Diffusing capacity for carbon dioxide (DLCO) less than 80% of predicted was reported in 53% (30/57)[46] and 47% (51/110)[33] of patients. Both studies also reported significant differences in DLCO for subgroups based on severity. In 1 study, DLCO was less than 80% predicted in 77% (13/17) of the severe cases and 43% (17/40) of the non-severe cases (P=.02).[46] In the other study, DLCO was <80% predicted for 84% (16/19) of the severe pneumonia subgroup, 42% (28/67) of the pneumonia subgroup, and 29% (7/24) of the mild subgroup (P<.01 for the severe pneumonia subgroup vs the pneumonia subgroup or the mild subgroup).[33] Another study reported that 26% (13/50) had altered diffusion capacity only, 18% (9/50) had restriction with altered diffusion

capacity, 8% (4/50) had restriction only, and 48% (24/50) had a normal pulmonary function test.[42]

Dyspnea

Measures of dyspnea were reported in 3 studies. Two used a modified Medical Research Council measure. One reported that 13% (4/32) were Grade 4 and 88% (28/32) were Grade 5 at the time of admission to a rehabilitation unit.[26] Grade 4 indicates a need to stop for breath after 100 meters or a few minutes on level ground while Grade 5 indicates too breathless to leave the house, or breathless after undressing (https://mrc.ukri.org/research/facilities-and-resources-for-researchers/mrc-scales/mrc-dyspnoea-scale-mrc-breathlessness-scale/). The second reported 29% (35/120) were at Grade 2 or higher at a mean of 111 days post-discharge. Grade 2 is described as "walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace".[43] The third study used the Borg scale and assessed dyspnea following the 6-minute walk test.[28] Values were generally less than 3 (*ie,* "moderate" dyspnea) on a 10 point scale. This study also reported the presence of exercise-induced hypoxia (defined as SpO_2 <90%) in 50% (13/26). Six of the patients underwent further testing and pulmonary embolism was confirmed in 67% (4/6).[28]

Other Outcomes

In 1 study of patients admitted to a rehabilitation unit, moderate alteration (values of 200-299 mmHg) in PaO_2/FiO_2 was observed in 38% (12/32) with severe (values <200 mmHg) alteration in 41% (13/32). Only 13% (4/32) did not require oxygen support.[26] Two studies reported findings from computed tomography (CT).[46,55] One reported residual abnormality on CT 30 days post-discharge in 54% (31/57), including 94% (16/17) in the severe subgroup and 38% (15/40) in the non-severe subgroup.[46] The other reported chest CT deterioration in 6% (2/36) at 1-2 weeks post-discharge but no deterioration in 54 patients evaluated with CT at 3-4 weeks.[55] Another study reported "lung abnormalities" (worsening or appearance of X-ray pulmonary infiltrates) in 85% (6/7) at the time of hospital discharge.[29] Patients in this study were all receiving maintenance hemodialysis at the time of hospitalization. Finally, 1 study used point of care ultrasound at discharge and observed pleural effusions in 1.5% (1/64).[22] At ICU admission, pleural effusions had been observed in 22.4% (20/89).

CARDIOVASCULAR OUTCOMES

Cardiovascular outcomes were reported in 4 studies (Appendix C, Tables 1 and 4) – 2 from Europe,[39,49] 1 from China,[45] and 1 from the Middle East.[22] Sample sizes range from 26 to 100, mean or median ages ranged from 38 to 50 years, and the percentage of males enrolled ranged from 38% to 84%. None of the studies reported hospital length of stay. Two studies included comparison groups.[45,49] All cardiovascular outcomes were based on imaging or laboratory assessments rather than clinical definitions or patient centered outcomes.

Two studies used cardiovascular magnetic resonance (CMR) imaging to assess myocardial injury. In a study from Germany, 100 patients were assessed at a median of 71 days following diagnosis.[49] 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 (age- and sex-matched, normotensive, taking no cardiac medications, with normal

cardiac volumes and function) and 57 risk factor-matched controls (matched for age, sex, hypertension, diabetes, smoking, known coronary artery disease, or comorbidities). From the CMR imaging, pericardial effusion (>10 mm) was observed in 20% (20/100) of the COVID-19 patients, 0% of the healthy controls, and 15% (9/57) of the risk factor-matched controls. The difference between the COVID-19 group and the other groups was statistically significant (P<.05). Late gadolinium enhancement (LGE), reflecting scarring, was observed in 32% (32/100) (myocardial) and 22% (22/100) (pericardial) of the COVID-19 group. Both were significantly more prevalent (P<.05) in the COVID-19 patients than in the healthy controls (0% for both measures) or the risk factor-matched controls (17% (9/57) with myocardial LGE and 15% (8/57) with pericardial LGE). Abnormal native T1 values were observed in 73% (73/100) of all COVID-19 patients with significantly higher values (P=.02) in those who had required hospitalization although the difference was characterized as small. Abnormal native T1 was reported in 6% (3/50) of the healthy controls and 40% (23/57) 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 noted between hospitalized and non-hospitalized patients. The prevalences were 4% (2/50) and 9% (5/57) in the healthy controls and risk factor-matched groups, respectively (both P<.05 vs the COVID-19 group). T1 and T2 generally reflect myocardial inflammation. The second study, from China, evaluated 26 patients referred for CMR due to cardiac symptoms post-discharge.[45] 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.

The study from Germany also reported blood test results.[49] Detectable high sensitivity troponin T (hsTNT) was reported in 71% (71/100) of the COVID-19 group with significantly elevated hsTNT in 5% (5/100). There was no significant difference in mean hsTNT values between the hospitalized and non-hospitalized groups. 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 (57% [31/57]).

A study from the United Kingdom, not yet peer-reviewed, reported left ventricular ejection fraction data for 37 previously hospitalized patients at a median of 105 days after COVID-19 diagnosis.[39] Definite impairment (<50%) was noted in 11% (4/37) and borderline impairment (50-55%) in 19% (7/27) while 70% (26/37) were normal (>55%). Evidence of myocarditis was noted in 11% (4/37).

A study from Saudi Arabia noted pericardial effusion on ultrasound at discharge in 1.5% (1/64 survivors) among 89 hospitalized with severe COVID-19.[22]

NEUROLOGICAL OUTCOMES

Six studies reported neurological outcomes (Appendix C, Tables 1 and 5).[21,23,30,32,35,43] Two were conducted in Europe,[23,43] 2 in the US,[30,32] and 2 in multiple nations.[21,35] Sample sizes ranged from 13 to 509, mean or median ages ranged from 58 to 76 years, and between 46% and 63% were male.

Modified Rankin Scale

Five studies reported modified Rankin Scale (mRS) results at the time of hospital discharge. An mRS score of 0 to 2 is considered a good outcome – individuals are "able to look after their own affairs without assistance". A multi-nation study enrolled patients who underwent mechanical thrombectomy following a stroke.[21] Symptomatic patients were tested for COVID-19. An mRS score of 0 to 2 was observed for 17% (2/12) in the COVID-19 group compared with 30% (94/316) in the non-COVID-19 group. The difference was not statistically significant (P=.52). A study from Italy reported outcomes for patients who had been admitted for acute cerebrovascular disease and tested positive for COVID-19.[23] An mRS score of 0-2 was noted for 26% (11/43) of the COVID-19 group and 71% (48/68) of the non-COVID-19 group (P<.001). A study from the US included 6 patients who were admitted for COVID-19 and subsequently experienced a stroke ('COVID' group) and 7 patients who were admitted for a stroke and subsequently diagnosed with COVID-19 ('neuro' group).[30] An mRS score of >2 (a 'poor' outcome) was reported for 77% overall (10/13), including 67% (4/6) in the 'COVID' group and 86% (6/7) in the 'neuro' group. In a control group of non-COVID-19 patients with stroke hospitalized during the same time period, a 'poor' outcome was noted in 47% (25/53) (P=.047 vs the overall study group). A second study from the US compared patients with and without neurological manifestations during hospitalization with COVID-19.[32] A history of neurological disorder was noted in 26% (134/509). An mRS score of 0 to 2 at discharge was reported for 71.4% (299/419) with neurological manifestations during hospitalization compared with 70.0% (63/90) with no neurological manifestations. Among patients with encephalopathy during hospitalization, 32,1% (52/162) had an mRS score of 0 to 2 compared with 89.3% (310/347) of those with no encephalopathy. Another multi-nation study reported severe disability in 51% (49 of 96 survivors).[35] 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).

NIH Stroke Scale

Two studies reported NIH Stroke Scale scores.[23,30] Scores range from 0 (no symptoms) and 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 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).[23] The study from the US reported median [IQR] scores of 11 [4-23] in the overall study group of 13 patients and 3 [2-13] in the non-COVID comparison group.[30]

RENAL OUTCOMES

Renal outcomes were reported by 3 studies (Appendix C, Tables 1 and 6), 2 from the US[24,34] and 1 from Europe.[39] The 2 studies from the US each reported on over 600 survivors while the study from Europe enrolled 37. Mean or median ages ranged from 50 to 71, with 38% to 79% male.

A study from the US reported acute kidney disease (AKD) at discharge in 25% (291/832).[24] 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. 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.

The second study from the US reported on 3,854 individuals who developed AKI while hospitalized for COVID-19.[34] Among those who required renal replacement therapy (RRT) while hospitalized, 17% (108/638) survived. Of the survivors, 33% (36/108) had not recovered kidney function and 92% (33/36) required RRT at 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 post-discharge in this group was not reported.

The study from Europe, not peer-reviewed, reported an imaging finding at a median of 105 days post-COVID-19 diagnosis.[39] Definite impairment on kidney cortex T1 was observed in 22% (8/37) with normal findings in 78% (29/37).

GASTROINTESTINAL OUTCOMES

The European study, noted above and not peer-reviewed, also reported liver imaging findings (Appendix C, Tables 1 and 7).[39] At a median of 105 days post-COVID-19 diagnosis, liver inflammation (cT1 in ms) was normal (<800 ms) in 84% (31/37), borderline (800-825 ms) in 0% (0/37), and significant (>825 ms) in 16% (6/37).

HEMATOLOGIC OUTCOMES

Three studies reported hematologic outcomes (Appendix C, Tables 1 and 8).[22,48,51] A study from Saudi Arabia reported the incidence of deep venous thrombosis (DVT) at discharge (determined with ultrasound) was 12.5% (8/64 survivors). All patients in this study had been admitted to intensive care and received mechanical ventilation. The median age was 43 and 84% were male.

The other 2 studies reported outcomes post-discharge. In a study from the US, at a median of 23 days post-discharge, thromboembolism was observed in 2.5% (4/163).[48] Twenty-six percent (42/163) had been hospitalized in the ICU. Events included pulmonary embolism (PE), intracardiac thrombus, thrombosed arteriovenous fistula, and ischemic stroke. At a median of 27 days post-discharge, 3.7% (6/163) experienced hemorrhagic events. 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 Europe reported venous thromboembolism (VTE) post-discharge.[51] Of 1877 included patients, 208 (11%) had been admitted to critical care. At a median of 8 days post-discharge, 0.48% (9/1877) experienced DVT (n=2) or PE (n=7). In a cohort of medical

admissions from 2019, 0.31% (56/18,159) experienced VTE events including 23 with DVT (8 proximal, 10 distal, and 5 line-associated upper-limb) and 33 with PE. The odds ratio for a VTE in the COVID-19 group was 1.6 (95%CI 0.77, 3.1) (P=.20).

HEALTHCARE/RESOURCE UTILIZATION OUTCOMES

Twenty-two studies – 13 from the US, 5 from China, and 4 from Europe – reported measures of healthcare and/or resource utilization (Appendix C, Tables 1 and 9).[25,27,30,31,36-38,40,41,44,47,48,50,52-57,60-62] Sample sizes ranged from 11 to 15,111 with 11 studies enrolling more than 100.[27,37,38,47,50,53,55,57,60-62] Mean or median ages ranged from 37 to 82; 1 study reported the range of ages (18 to 85).[36] Between 27% and 71% were male. COVID-19 severity was reported in 7 studies; 2 only enrolled severe[47] or critically ill[56] patients. Median hospital length of stay ranged from 2 to 24 days.)

Discharge Disposition

Eleven studies reported on discharge disposition.[25,27,30,31,36,37,50,55,60-62] Three studies enrolled patients with stroke or other neurological conditions.[30,31,36] 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).[30] Another 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.[31] 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.[31] The third 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.[36]

One US study enrolled 20 patients with HIV who were hospitalized for COVID-19; 4 patients (20%) were from a VA Medical Center.[25] Of patients discharged, 81% (13/16) were discharged home, 6% (1/6) 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, 1 in a substance abuse recovery home).

Another study from the US included 2 comparison groups: patients negative for COVID-19 and a historical control group.[27] Among those who tested positive for COVID-19 and were discharged, 77% (1650/2142) were discharged home and 23% to a nursing home (492/2142). Among patients negative for COVID-19 and discharged, 83% were discharged home (788/950) and 17% (162/950) to a nursing home. In the historical control group, 85% (8108/9544) were discharged home and 15% (1436/9544) to a nursing home. It was noted that 16% of patients were nursing home residents prior to hospitalization.

Two US studies provided data for subgroups based on treatment location[62] or age.[50] In the first study, of patients treated in the general practice unit and with known discharge disposition, 96% (183/191) went home and 4% (8/191) went to a rehabilitation center.[62] Of patients treated in the ICU and with known discharge disposition, 79% (49/62) went home and 21% (13/62) went to a rehabilitation center. In the second study, 6% (122/2081) of patients discharged alive were discharged to a "facility" (*eg*, nursing home, rehabilitation).[50] The total included 0% (0/32) of those under 18 years, 2% (28/1,373) of those 18 to 65 years, and 14% (94/676) of those over age 65. Ninety-four percent (1959/2081) were discharged home.

Two studies from the United Kingdom with similar patient demographics and hospital lengths of stay reported that 81.0% (56/69)[61] and 93% (614/664)[37] of patients discharged were discharged to home; and 14.0% (10/69)[61] and 5.1% (34/664)[37] were discharged to care homes. In 1 study, it was reported that 7.2% (5/69) were new care home placements.[61]

A study from China provided information at up to 4 weeks post-discharge.[55] At 1-2 weeks post-discharge, 87% (114/131) were in home quarantine, 9% (12/131) in community quarantine, 4% (5/131) in a "designated hospital", and 0% had returned to work. At. 3-4 weeks post-discharge, the values were 92% (121/131), 3% (4/131), 2% (3/131), and 2% (3/131), respectively.

One US study reported discharge disposition for patients who had been readmitted.[60] Of 19 readmitted, 5 (26%) were discharged to a skilled nursing facility and 14 (74%) either to home or a hotel for homeless persons experiencing COVID-19.

Hospital Readmission

Hospital readmission for any reason was reported by 12 studies.[38,40,41,47,48,50,52,53,55,60-62] Mean or median duration of follow-up to assess readmission ranged from 3 to 40 days; several studies did not report length of follow-up. The 2 largest studies were from Spain[38] and the US.[53] In the study from Spain, 4.8% (573/11,928) were readmitted.[38] Median follow-up was 40 days post-discharge. Over 5% (31/573) of readmitted patients remained hospitalized through the follow-up period. Reason for readmission was not provided. In the US study, with a 14 day follow-up, 3.6% (103/2864) returned for emergency care.[53] Of those, 54.4% (56/103) were admitted. The most frequently reported reasons for readmission included respiratory distress (60%), chest pain (6%), other pain (6%), altered mental status (5%), fall (5%), and soft tissue infection (5%). ICU-level care was required for 10.7% (6/56).

Comparison groups were included in 2 studies from the US.[40,41] In the first study, enrolling patients undergoing surgery for hip fracture, within 30 days of discharge, 11.8% (2/17) of COVID-19 positive patients had been readmitted compared with 2.8% (3/107) COVID-19 negative patients.[40] In the second study, 11% (9/92) patients were readmitted in both the COVID-19 acute respiratory distress syndrome (ARDS) group and a propensity match group with non-COVID-19 ARDS.[41] The length of follow-up post-discharge and reasons for readmission were not reported.

Another US study enrolled patients with severe ARDS.[47] Readmission rates ranged from 5 to 10% with no difference between those who also had asthma and those who did not in either the 21 to 39 year age group or the 40 to 65 year age group. Length of follow-up was not reported.

Readmission rates in different age groups were also reported in another US study.[50] After a median follow-up of 4.4 days, a total of 2.2% (45/2081) were readmitted including 3% (1/32) of those under 18 years, 2% (22/1,373) of those 18 to 65 years, and 3% (22/676) of those over age 65. The median time to readmission was 3 days.

Suleyman et al, a US study, reported 30-day hospital readmission was 11% (29 patients).[62] This included 27 patients who had been treated in the general practice unit and 2 patients treated in the ICU.

In 5 other studies, readmission rates ranged from 4% to 9%.[48,52,55,60,61] Three of the studies were from the US, 1 from the United Kingdom, and 1 from China. One of the US studies reported reasons for readmission.[60] Bacterial pneumonia secondary to COVID-19 was documented in 21% (4/19), a prolonged COVID-19 course in 21% (4/19), psychiatric episodes in 16% (3/19), metabolic encephalopathy in 11% (2/19), and thrombotic episodes in 11% (2/19).

Positive SARS-CoV-2 Post-Discharge

Five studies reported on patients with positive tests for SARS-CoV-2 following hospital discharge.[44,54,55,57,60] One US study, reported that 63% (12/19) tested positive at the time of readmission.[60] The remaining studies were from China.[44,54,55,57] In 1 of the studies, patients were isolated and monitored for 28 days post-discharge.[54] Another required 14 days quarantine and requested hospital visits every 2-4 weeks.[57] The third asked patients to follow-up every 7 days for 4 weeks.[55] The fourth included 2-4 week follow-up to assess short-term outcomes post-discharge.[44] Positive tests were reported in 2% to 28% of patients at follow-up times to 4 weeks post-discharge.

Post-discharge Treatment

Use of oxygen therapy ranged from 6% to 7% in 2 studies reporting. One study reported that 6% (5/85) were receiving oxygen therapy via nasal cannula at home (time post-discharge not specified).[56] Wang et al reported that at 1-2 weeks after discharge 7% (9/131) were treated with oxygen therapy.[55] 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 US study reported need for post-acute rehabilitation in patients undergoing surgery for hip fracture.[40] 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).

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).[61]

DISCUSSION

Our review identified 42 reports of post-acute major organ damage or healthcare/service use outcomes in patients who were hospitalized with or for COVID-19. Eighteen studies were from the US; 1 multisite US study included patients from a VA Medical Center. The amount of data is increasing rapidly. We identified an additional 25 studies in the 2.5-month interval from our

original July search date. Future updates are likely to identify relevant new data. We provide "Key Findings", "Limitation", and "Suggestions for Future Research".

KEY FINDINGS

Key Question 1

We identified limited published *post-hospital* data on conditions reported to be associated with COVID-19 during hospitalization including pulmonary, cardiovascular, gastrointestinal, hematologic/thrombotic, neurologic, or renal. Available evidence suggests:

- Pulmonary fibrosis in 7% to 44%, pulmonary function below thresholds in 9% to 25%, and diffusing capacity for carbon dioxide "altered" or below threshold in 47% to 53%,
- Impaired cardiovascular ejection fraction in 11% and LGE abnormalities in 22% to 32%,
- Moderate-to-severe stroke sequelae in 29% to 83%,
- Thromboembolism in 0.5% to 12.5%, and
- AKD in 28% to 35%.

We found no published *post-hospital* information for metabolic/endocrine or rheumatologic/musculoskeletal conditions.

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,* treatment for COVID-19). Few studies reported outcomes for subgroups of patients.

Key Question 3

Discharge disposition (other than home: 7% to 65%) and readmission (2% to 12%) were frequently reported outcomes. There was little or no information about other healthcare/resource use outcomes 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:

- 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; 11 studies included control groups for comparison of COVID-19 and non-COVID-19 patients.
- Major organ damage measures were not standardized and varied considerably across studies. Reported prevalence rates are likely highly dependent on the measures used to assess and define major organ damage as well as the population being evaluated.

- Most 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.
- The contribution of comorbidities (prior to COVID-19 infection) to post-acute prevalence cannot be determined.

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 October 6, 2020 and would not have included information published after that date. Ongoing living review rapid review methods are needed to capture additional information.

FUTURE RESEARCH

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

Population

We chose to define post-acute as post-hospitalization but other definitions may be appropriate. 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).[63] 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 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 also likely underestimates the burden of post-acute complications when also including patients with suspected COVID-19. 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, type of residence (*eg,* independent living, assisted living, nursing home), COVID-19 severity, 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 would allow for a better understanding of the effects of COVID-19. Without appropriate comparators and information on pre-COVID conditions it is not possible to accurately determine the effect that COVID-19 has on post-acute health outcomes or the incremental effects versus controls without COVID-19. Nonetheless, given ongoing health and health care 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 should include standardized and longer follow-up.

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)
- Aa 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.[63]

- 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.[64]

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), 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.[65-74] 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,[15] 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 of the literature yielded limited early published data on post-acute COVID-19 major organ damage and healthcare/service use needs. The majority of studies were from outside the United States; only 1 study enrolled patients from a VA Medical Center. There was little information on patient-centered, clinical health outcomes. Available data are from studies of convenience samples with poorly described study populations and primarily physiologic outcomes; few included control groups for comparison of COVID-19 and non-COVID-19 patients. Studies of pulmonary function were most common and, although there were reports of pulmonary fibrosis, imaging abnormalities, and reduced pulmonary function, interpretation is difficult due to the absence of pre-COVID-19 data. Future research should attempt to include clear descriptions of the patient populations and the timing of outcome assessment with respect to hospitalization, link pre-COVID-19 data with post-COVID-19 data, and 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.

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