Brief Summary of Findings on the Association Between a History of Pulmonary Embolism or Pulmonary Hypertension and Severe COVID-19 Outcomes

Prepared and reviewed by:

Marwan Wassef, MPH; Data Analyst; Chenega Corporation

David Weissman, MD, Director Respiratory Health Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (CDC)

Jacek Mazurek, MD, MS, PhD, Branch Chief, Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, CDC

Girija Syamlal, MBBS, MPH, Research Epidemiologist, Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, CDC

Katelynn Dodd, MPH, Associate Service Fellow, Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, CDC

Mylaica Conner Henry, MPH; Communications Specialist/Technical Writer; Eagle Global Scientific

Jill K. Kumasaka; ORISE Fellow; Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, CDC

Devon L. Okasako-Schmucker, MPH; Program Analyst; Eagle Global Scientific

Tashika M. Robinson, MPH; Program Analyst III; Eagle Global Scientific, LLC

Christine Nam So, MPH; Program Analyst III; Eagle Global Scientific

Madelon Morford, MPH, Public Health Analyst, General Dynamics Information Technology

Kristen Tansil Roberts; MSW; Behavioral Scientist; Division of HIV/AIDS Prevention, Prevention Research Branch, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC

Erin C. Stone, MPH, MA; Public Health Analyst; Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, CDC

Joanna Taliano, MA, MLS; Reference Librarian, Cherokee Nation Assurance

David A Siegel, MD MPH, Core Clinical Unit, Clinical Disease and Health Services Team, Health Systems and Worker Safety Task Force, CDC COVID-19 Response, CDC

Emily Koumans, MD MPH, Clinical Disease and Health Services Team Lead, Health Systems and Worker Safety Task Force, CDC COVID-19 Response, CDC

Kanta Devi Sircar, PhD, MPH, Epidemiologist, Underlying Conditions, Core Clinical Unit, Clinical Disease and Health Services Team, Health Systems and Worker Safety Task Force, CDC COVID-19 Response

Contact: CDC Info contact us form

Brief Summary of Findings on the Association Between Underlying Pulmonary Embolism and Severe COVID-19 Outcomes

One cohort study[1] was retrieved that reported data on patients with a history of pulmonary embolism and severe COVID-19 outcomes.

- Limited evidence from one cohort study[1] suggests that a history of pulmonary embolism is associated with an increase in the risk of mortality. However, one study is insufficient to definitively conclude an increase in risk and new evidence may change these conclusions.

Brief Summary of Findings on the Association Between Underlying Pulmonary Hypertension and Severe COVID-19 Outcomes

Three cohort studies[1-3] were retrieved that reported data on patients with a history of pulmonary hypertension and severe COVID-19 outcomes.

- Limited evidence suggests that underlying pulmonary hypertension is associated with an increase in the risk of mortality[1, 2] , ICU admission[2], and hospitalization[3]. However, one study is insufficient to definitively conclude an increase in risk and new evidence may change these conclusions for ICU admission and hospitalization.

Contents

Table of Tables

A. Methods

The aim of this review is to identify and synthesize the best available evidence on the association between Pulmonary Embolism or Pulmonary Hypertension and severe COVID-19 in order to update the Centers for Disease Control and Prevention (CDC) website on underlying conditions for a consumer and a provider-specific website with more rigorous information.

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, and outcomes (PECO) question. Clinical experts and library scientists were consulted to develop a robust list of search terms. These terms were then incorporated into search strategies, and these searches were performed in OVID using the COVID-19 filter from the end of the previous literature search (December 2020). The detailed search strategies for identifying primary literature and the search results are provided in Part B. Subject matter experts supplemented the literature search results by recommending relevant references published before December 2020. References were included if retrieved by the chronic lung disease literature search and reported exposures and outcomes relevant to this review.

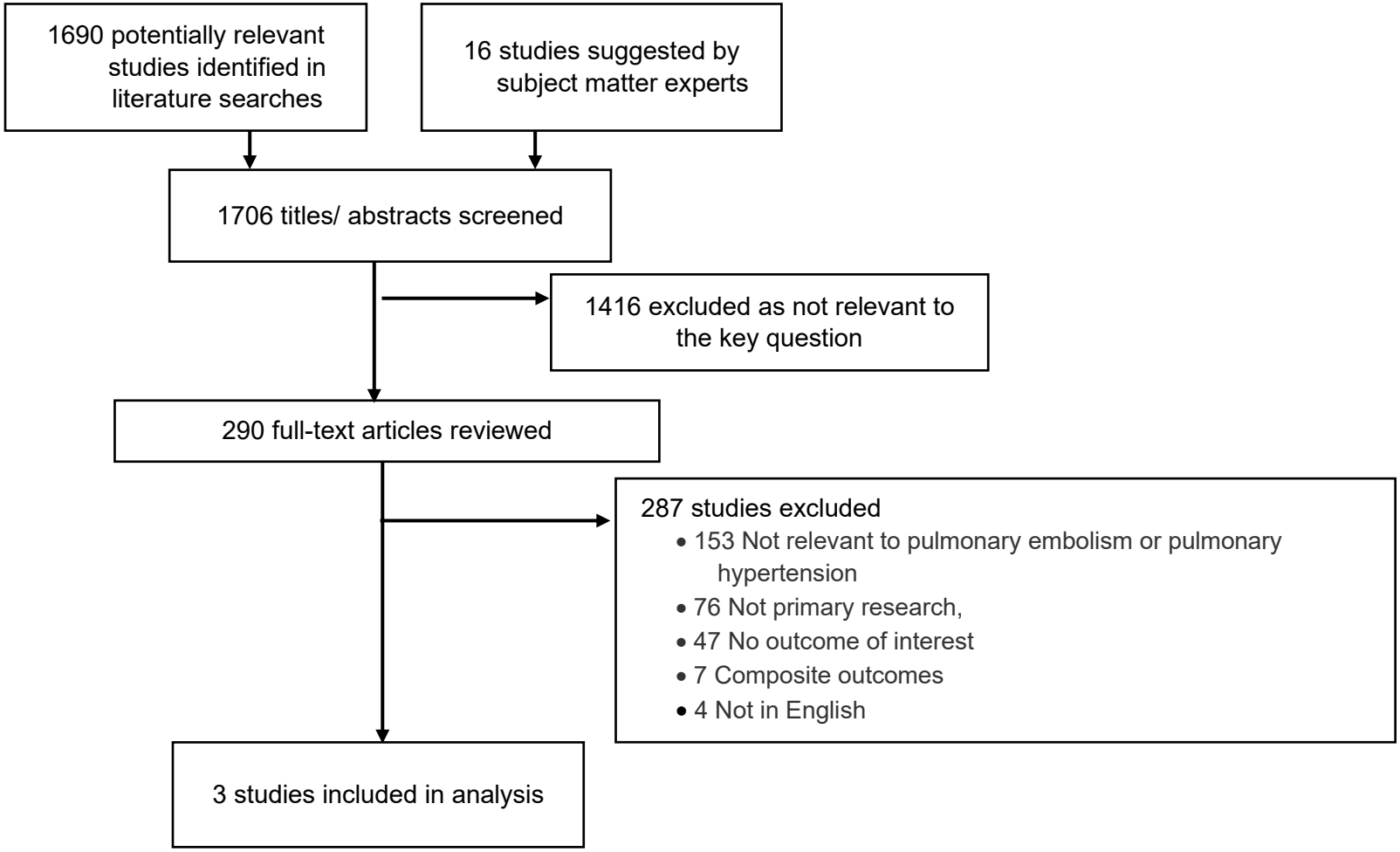
A.2. Study Selection

Titles and abstracts from references were screened by dual review (initials: M.C., J.K.K., C.O., D.O.S., T.R., C.S., E.C.S., or M.W.). Full-text articles were retrieved if they were:

1. relevant to the PECO question;
2. primary research, and
3. written in English.

Part B presents the full list of exclusion criteria. The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (initials: J.K.K., D.O.S., K.T.R., C.S., E.C.S., or M.W.). After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with subject matter experts. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in Figure 1.

Figure 1. Results of the Study Selection Process



A.4. Data Extraction and Synthesis

Methodologic data and results of relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review, statistical significance was defined as $p \leq 0.05$.

A.5. Aggregation of the Evidence

The internal validity associated with each study was assessed using scales developed by the Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. Part B includes the questions used to assess the quality of each study design. The strength, magnitude, precision, consistency, and applicability of results were assessed for all comparators. The overall confidence in the evidence base is reported in the aggregation tables in Part B.

A.6. Reviewing and Finalizing the Systematic Review

Draft findings, aggregation tables, and evidence tables, are presented to CDC subject matter experts for review and input. Following further revisions, the summary will be published on the CDC website.

B. Systematic Literature Review Results

B.1. Search Strategies and Results

Table 1 Chronic Lung Disease Search Conducted March 17, 2021

#	Search History
1	chronic lung disease
2	respiratory system disease*
3	reactive airway disease*
4	emphysema
5	chronic bronchitis
6	COPD
7	Chronic obstructive pulmonary disease
8	Asthma *
9	allergic asthma
10	irritant asthma
11	Interstitial lung disease
12	Pulmonary fibrosis
13	idiopathic pulmonary fibrosis
14	nonspecific interstitial pneumonitis
15	hypersensitivity pneumonitis
16	sarcoidosis
17	pneumoconiosis
18	asbestosis
19	coal workers pneumoconiosis
20	silicosis
21	bronchiectasis
22	cystic fibrosis
23	pulmonary vascular disease

24	pulmonary hypertension
25	bronchopulmonary dysplasia
26	bronchiolitis obliterans
27	asthma*
28	reactive airway disease*
29	CF
30	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	Limit 30 to covid-19
32	(202012* or 2021*).dt
33	(202012* or 2021*).dc
34	32 or 33
35	31 and 34
36	Deduplicate

B.2. Study Inclusion and Exclusion Criteria

Inclusion Criteria: Studies were included at the title and abstract screen if they:

- were relevant to the key question "what is the association between pulmonary embolism or pulmonary hypertension and severe COVID-19?";
- were primary research;
- were written in English (can be seen as [language] in title); and
- examined humans only.

Exclusion Criteria: Studies were excluded at full text review if they:

- were not available as full-text;
- were a conference abstract, poster, letter to the editor, or reply letter;
- examined lung transplant, cancer, or immunocompromised populations;
- reported autopsy results; and
- reported only composite outcome measures for "severe COVID-19".

B.3. Evidence Review: Pulmonary Embolism or Pulmonary Hypertension and Severe COVID-19

B.3.a. Strength & Direction of Evidence

Table 2. The Association Between Pulmonary Embolism and Severe COVID-19 Outcomes Including Mortality.

Outcome	Results
Mortality:	Overall, the limited evidence from only one study[1] suggests a history of pulmonary embolism is associated with an increased risk of mortality. Aggregation indices cannot be measured with only one study which was found to have a moderate threat to internal validity. ▪ One cohort study[1] (N = 16,709), of 940 patients with pulmonary embolism conducted a multivariable analysis adjusted for demographic factors such as age, sex, race, and the presence of other comorbidities. There was a higher odd of mortality for people with COVID-19 and a history of pulmonary embolism, compared to people with COVID-19 and no history of pulmonary embolism [aOR: 1.02 (IQR: 0.02)].

Table 3. The Association Between Pulmonary Hypertension and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Overall, the evidence from two studies[1, 2] suggests the presence of underlying pulmonary hypertension is associated with an increased risk or adjusted odds of mortality. Both studies were found to have a moderate threat to internal validity. • Strength of Association: Measures of association ranged from adjusted values of 1.24 to unadjusted values of 4.91. • Precision of Association: Confidence intervals are wide in both studies, and crossed the null in one study[2] . • Consistency of Association: Both measures of association suggested a positive association. • Applicability of Association: The population and setting were applicable in both studies. Two cohort studies[1, 2] (N = 106,239) suggested an increase in the risk or adjusted odds of mortality in patients with underlying pulmonary hypertension. ▪ One cohort study[1] (N = 16,709), of 322 patients with pulmonary hypertension conducted a univariable analysis and reported an increased in the unadjusted risk of mortality for people in the US with COVID-19 and a history of pulmonary hypertension, compared to people without underlying pulmonary hypertension [RR: 4.91 (95% CI: 3.96 – 6.07)]. In a multivariable analysis, pulmonary hypertension did not persist as an independent risk factor in either an overall analysis or the age-stratified analysis that excluded patients younger than 45 years of age. In the age-stratified analysis excluding people less than 45 years of age, there was an increase in the adjusted odds of mortality for people with underlying pulmonary hypertension aged 45-65 years [aOR: 1.04 (IQR: 0.02)]; and 65-85 years [aOR: 1.04 (IQR: 0.02)]; however, this risk did not persist for those over 85 years of age. ▪ One cohort study[2] (N = 89,530), of 341 hospitalized patients in France with pulmonary hypertension conducted a multivariable analysis adjusting for obesity, diabetes, hypertension, heart failure, atherosclerotic heart disease, sex, and age as a continuous variable. Results suggested an increase in the adjusted odds of mortality among hospitalized patients with COVID-19 and underlying pulmonary hypertension compared to patients with no underlying pulmonary hypertension [aOR: 1.24 (95% CI: 0.91-1.67)]; however, the confidence interval crossed the null, reducing confidence in the strength of this association.
ICU admission	One cohort study[2] reported an increase in ICU admission for patients with underlying pulmonary hypertension. Aggregation indices cannot be measured with only one study which was found to have a moderate threat to internal validity.

	▪ One cohort study[2] (N = 89,530), of 341 hospitalized patients in France with pulmonary hypertension conducted a multivariable analysis adjusting for obesity, diabetes, hypertension, heart failure, atherosclerotic heart disease, sex, and age as a continuous variable. Results suggested an increase in the adjusted odds of ICU admission among hospitalized patients with COVID-19 and underlying pulmonary hypertension compared to patients with no underlying pulmonary hypertension [aOR: 1.73 (95% CI: 1.27-2.37)].
Hospitalization	One cohort study[3] reported no association between pulmonary hypertension disease and hospitalization. Aggregation indices cannot be measured with only one study which was found to have a moderate threat to internal validity. ▪ One cohort study[3] (N = 821), of people with COVID-19, reported zero hospital admissions among patients with those with underlying pulmonary hypertension compared to those with COVID-19 only (0/8 vs. 3/86). The small number of events in this study limits the applicability of this data.

B.3.b. Extracted Evidence

Table 4 Extracted Studies Reporting the Association Between Pulmonary Embolism or Pulmonary Hypertension and Severe COVID-19 Outcomes

Study	Population and Setting	Intervention	Definitions	Results
Author: Beltramo [2] **Year:** 2021 **Data Extractor:** MC **Reviewer:** DOS **Study design:** Cohort **Study Objective:** To describe and compare chronic respiratory diseases (CRD) in hospitalized patients suffering from COVID-19	**Population:** N = 89,530 COVID-19 patients **Setting:** Public and private hospitals **Location:** France **Study dates:** COVID-19 cohort: March 1 - April 30, 2020 **Inclusion criteria:** For the COVID-19 cohort, all patients hospitalized for COVID-19 during the study dates were included and identified by the primary, related, or	**Health Condition Category:** Chronic lung disease **Medical Condition, n/N (%):** Pulmonary hypertension: 341/89,530 (0.38%) **Control/Comparison group, n/N (%):** No CRD: 75179/89530 (84.0%)	**Medical Condition(s):** *Pulmonary hypertension*: ICD-10 I270 **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy, n/N (%):** NR **Outcome Definitions:** *Mortality:* in-hospital mortality during hospitalization *ICU admission:* ND *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** none	**Severe COVID-19:** *aOR: Adjusted odds ratio; adjusted for obesity, diabetes, hypertension, heart failure, atherosclerotic heart disease, sex, and age as a continuous variable* *OR: Odds ratio* *Mortality, n/N (%):* Pulmonary hypertension: • aOR: 1.24 (95% CI: 0.91-1.67) • OR: 2.01 (95% CI: 1.50-2.68) • Pulmonary hypertension: 96/341 (28.2%) • No CRD: 11222/75179 (14.93%) • p<0.05 *ICU admission, n/N (%):* Pulmonary hypertension: • aOR: 1.73 (95% CI: 1.27-2.37) • OR: 1.97 (95% CI: 1.46-2.65) • Pulmonary hypertension: 97/341 (28.5%) • No CRD: 12119/75179 (16.12%) • p<0.05

Study	Population and Setting	Intervention	Definitions	Results
or influenza (2018-2019 season), and to describe and compare respiratory complications for COVID-19 patients with CRD to COVID-19 patients without CRD and to influenza patients. **IVA Score:** 24 (moderate)	associated diagnoses by the ICD-10 codes U0710, U0711, U0712, U0714 or U0715, regardless of their age. Data obtained from the national Programme de Medicalisation des Systemes d'Information (PMSI) database. **Exclusion criteria:** NR			**Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Estiri[1] **Year:** 2021 **Data Extractor:** DOS **Reviewer:** MW **Study design:** Cohort **Study Objective:** To predict risk of mortality and study risk factors for death across	**Population:** N = 16,709 **Setting:** Medical system consisting of 10 hospital **Location:** MA, US **Study dates:** March 3 - November 10, 2020 **Inclusion criteria:** EHR data from patients with a confirmed case for COVID-19 (confirmed PCR test) who had at least 1 year of	**Medical Condition, n/N (%):** Pulmonary hypertension: 322/16,709 (1.9%) Pulmonary embolism: 940/16,709 (5.6%) **Control/Comparison group, n/N (%):** No pulmonary hypertension: 16387/16709 (98.1%) No pulmonary embolism: 15769/16709 (94.4%)	**Medical Condition(s):** *Pulmonary hypertension:* ICD9 416.0; ICD10 I27.x *Pulmonary embolism:* ICD9 415.x, 453.x, 445.x, 673.x; ICD10 I26.x, I74.x, I75.x, I82.x, O88.x, Z86.711, Z86.718 **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* from various data sources and included mortality unrelated to visit	**Severe COVID-19:** *aOR: Adjusted odds ratio from GLM boosting model; median over 10 model iterations; model included age, history of pneumonia, type 2 diabetes mellitus with complications, heart failure, chronic kidney disease, interstitial pulmonary disease, chronic obstructive pulmonary disease, pulmonary embolism, benign prostate hypertrophy, atrial fibrillation and flutter, hypertensive urgency or emergency, coronary artery disease, gout, lung neoplasm, history of a cerebrovascular accident, abdominal aortic aneurysm, cardiomegaly, and female* *RR: risk ratio* *OR: odds ratio* *Mortality, n/N (%):* Pulmonary hypertension:

Study	Population and Setting	Intervention	Definitions	Results
different age groups. **IVA Score:** 25 (moderate)	medical history (i.e., a 1-year time difference between the first and last medical record before the COVID-19 positive PCR test) with medical system. Included data from beginning of electronic record (as far back as January 1, 2020) up to 14 days prior to the positive COVID-19 PCR test date. **Exclusion criteria:** NR		*ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	• RR: 4.91 (95% CI: 3.96-6.07) • OR: 6.06 (95% CI: 4.59-7.91) • Non-survivors: 73/830 (8.8%) • Survivors: 249/15,879 (1.6%) • p<0.001 Pulmonary embolism: • aOR: 1.018 (IQR: 0.019) • RR: 3.55 (95% CI: 3.01-4.19) • OR: 4.02 (95% CI: 3.30-4.86) • Non-survivors: 145/830 (17.5%) • Survivors: 795/15,879 (5.0%) • p<0.001 **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Halalau[3] **Year:** 2021 **Data Extractor:** MW **Reviewer:** DOS **Study Design:** Cohort	**Population:** N = 821 **Setting:** Large healthcare system including 8 hospitals **Location:** Michigan, USA **Study dates:** Up to April 12, 2020	**Health Condition Category:** Chronic Lung Disease **Medical Condition, n/N (%):** Pulmonary hypertension: 8/821 (1%) **Control/Comparison group, n/N (%):** None of the above: 295/821 (35.9%)	**Medical Condition(s):** *Pulmonary hypertension:* ND **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* NR	**Severe COVID-19:** *Hospitalization, n/N (%):* Pulmonary hypertension: • Admitted patients: 0/86 (0%) • Outpatients: 8/735 (1.1%) • p = 1.0 **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR

Study	Population and Setting	Intervention	Definitions	Results
Study Objective: To describe the demographics, initial clinical presentation, and outcomes of a large cohort of outpatients with COVID-19. **IVA Score:** 23 (moderate)	**Inclusion criteria:** Patients who tested positive for SARS-CoV-2 at any date up to April 1, 2020, after evaluation at any of the emergency departments across the 8 study hospitals, and subsequently discharged home. Laboratory confirmation for COVID-19 was defined as a positive result of real-time RT-PCR assay of nasopharyngeal swabs. Testing was offered if patients experienced moderate cough or fever over 100.4°F, and if they had chronic kidney disease, heart disease, diabetes, chronic lung disease, were receiving immunosuppression medication, or were immunocompromised due to cancer treatment, recent		*ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* Emergency department visits for the patients that resulted in admission to hospital *Non-elective readmissions*: NR **Comments:** None	**Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR

Study	Population and Setting	Intervention	Definitions	Results
	surgeries, or other conditions. **Exclusion criteria:** All patients with a negative test for SARS-CoV-2.			

B.3.c. Internal Validity Assessments of Extracted Studies

Table 5. Internal Validity Assessments of Extracted Studies Reporting the Association Between Pulmonary Embolism or Pulmonary Hypertension and Severe COVID-19 Outcomes

	Author Year	Beltramo 2021[2]	Estiri 2021[1]	Halalau 2021[3]
	Outcome	Mortality, ICU admission	Hospitalization	Hospitalization
Domain	**Signaling question**	Data extracted from hospital records	medical records	Data extracted from electronic medical records
Study Elements	Design appropriate to research question	1	1	1
	Well described population	1	1	1
	Well described setting	1	1	1
	Well described intervention/ exposure	1	1	1
	Well described control/ comparator	1	1	1
	Well described outcome	1	1	1
	Clear timeline of exposures/ interventions and outcomes	0	1	1
Selection Bias: Sampling	Randomization appropriately performed	0	0	0
	Allocation adequately concealed	0	0	0

	Author Year	Beltramo 2021[2]	Estiri 2021[1]	Halalau 2021[3]
	Outcome	Mortality, ICU admission	Hospitalization	Hospitalization
Domain	**Signaling question**	Data extracted from hospital records	medical records	Data extracted from electronic medical records
	Population sampling appropriate to study design	1	1	1
Selection Bias: Attrition	Attrition not significantly different between groups	1	1	1
	Attrition <10-15% of population	1	1	1
	Attrition appropriately analyzed	1	1	1
Information Bias: Measurement and Misclassification	Measure of intervention/ exposure is valid	1	1	1
	Measure of outcome is valid	1	1	1
	Fidelity to intervention is measured	0	0	0
	Fidelity to intervention is valid	0	0	0
	Prospective study	1	1	1
	Adequately powered to detect result	0	1	0
Information Bias: Performance & Detection	Outcome assessor blinded	0	0	0
	Study participant blinded	0	0	0
	Investigator/ data analyst blinded	0	0	0
	Data collection methods described in sufficient detail	1	1	1
	Data collection methods appropriate	1	1	1
	Sufficient follow up to detect outcome	1	1	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	1	1	1
	Appropriate statistical analyses are conducted correctly	1	1	1
	Confidence interval is narrow	1	0	0
Confounding	Potential confounders identified	1	1	1
	Adjustment for confounders in study design phase	0	0	0
	Adjustment for confounders in data analysis phase	1	1	0

	Author Year	Beltramo 2021[2]	Estiri 2021[1]	Halalau 2021[3]
	Outcome	Mortality, ICU admission	Hospitalization	Hospitalization
Domain	**Signaling question**	Data extracted from hospital records	medical records	Data extracted from electronic medical records
Reporting Bias	All pre-specified outcomes are adequately reported	1	1	1
Other Bias	No other sources of bias	1	1	1
COI	Funding sources disclosed and no obvious conflict of interest	1	1	1
SCORE	Threat to internal validity	24	25	23
	Low, Moderate, High	Moderate	Moderate	Moderate

C. References

1. Estiri H, Strasser ZH, Klann JG, Naseri P, Wagholikar KB, Murphy SN. Predicting COVID-19 mortality with electronic medical records. *npj Digital Medicine*. 2021;4(1)15. doi:http://dx.doi.org/10.1038/s41746-021-00383-x

2. Beltramo G, Cottenet J, Mariet A-S, et al. Chronic respiratory diseases are predictors of severe outcome in COVID-19 hospitalised patients: a nationwide study. *European Respiratory Journal*. 2021:2004474. doi:10.1183/13993003.04474-2020

3. Halalau A, Odish F, Imam Z, et al. Epidemiology, Clinical Characteristics, and Outcomes of a Large Cohort of COVID-19 Outpatients in Michigan. *Int J Gen Med*. 2021;14:1555-1563. doi:10.2147/ijgm.S305295

D. Abbreviations

Acronym	Full
95% CI	95% confidence interval
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
BMI	body mass index
BPD	bronchopulmonary dysplasia
CF	cystic fibrosis

CFR	case fatality ratio
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
ECMO	extracorporeal membrane oxygenation
EHR	electronic health record
EMR	electronic medical record
ERT	evidence review team
IQR	Interquartile range
GLM	generalized linear model
HH	high-high counties
HR	hazard ratio
ICD10	International Classification of Diseases 10
ICNARC	Intensive Care National Audit and Research Centre
ICS	inhaled corticosteroids
ICU	intensive care unit
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IVA	Internal validity assessments
LL	low-low counties
MR	mortality Rate
ND	not defined
NR	not reviewed
OR	odds ratio
PCR	polymerase chain reaction
PECO	population, exposure, comparator, and outcomes
PMSI	Programme de Medicalisation des Systemes d'Information
RR	Rate ratio
RT-PCR	real-time polymerase chain reaction