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

Prepared and reviewed by:

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

David Weissman, MD, Director Respiratory Health Division, National Institute for Occupational Safety and Health, 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 LLC

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, LLC

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

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

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

Marwan Wassef, MPH; Data Analyst; Chenega Corporation

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

Four cohort studies were retrieved that reported data on severe COVID-19 outcomes for people with bronchiectasis.

- The evidence[1-3] suggests an increase in the risk of mortality and intensive care unit (ICU) admission[1, 2] for people with underlying bronchiectasis. Limited evidence suggests an increase in the risk of hospitalization[1] and a protective effect for intubation[1]; however, one study is insufficient to definitively conclude a change in risk and new evidence may change these conclusions.

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A. Methods

The aim of this review was to identify and synthesize the best available evidence on the association between Bronchiectasis and severe COVID-19 outcomes 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 Section B.1. 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.

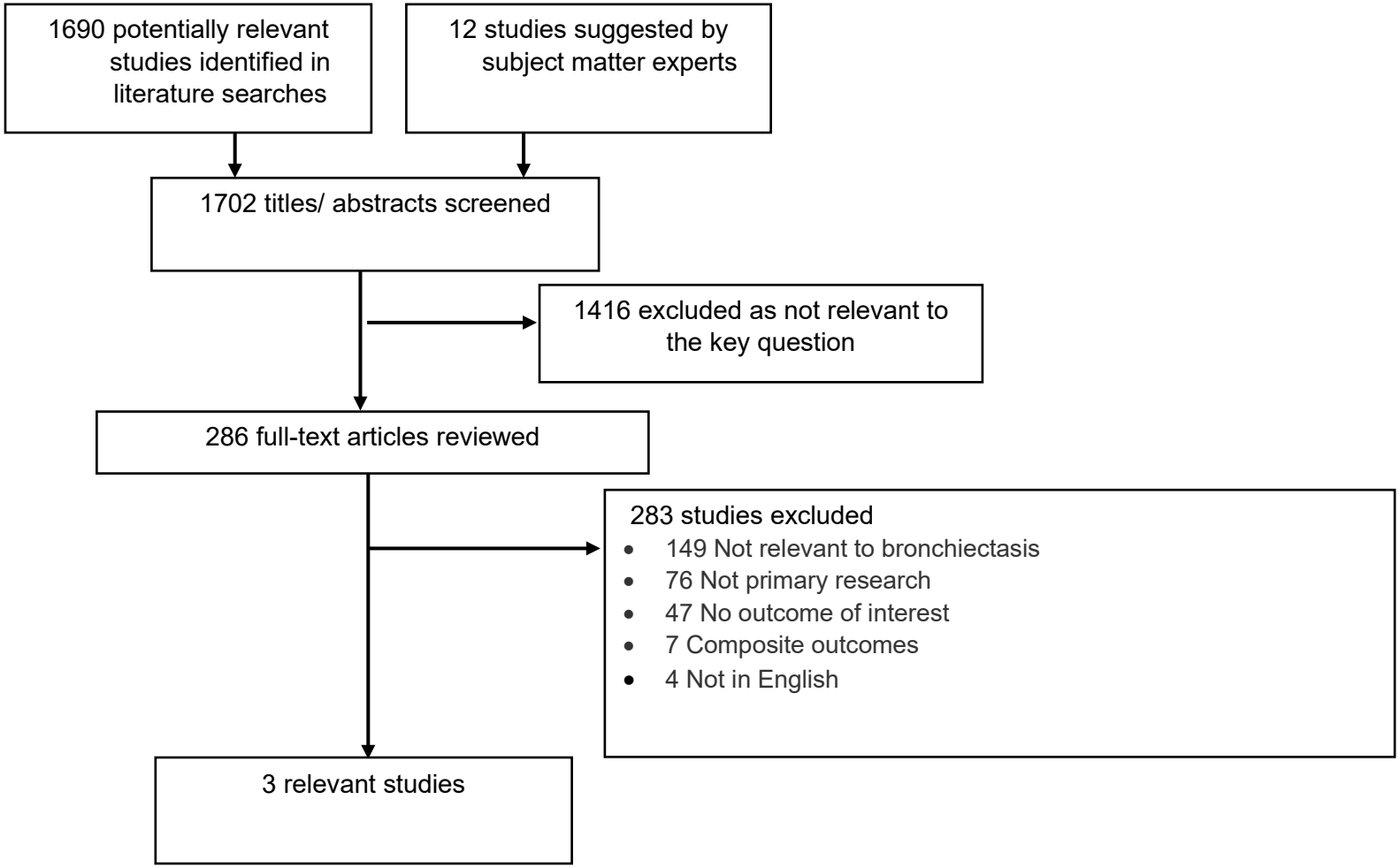
A.2. Study Selection

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.

Section B.2 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., C.O., 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.3. 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.4. 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. Table 4 in Section B.3.c. includes the signaling 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 Section B.3.a.

A.5 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 bronchiectasis and severe COVID-19 outcomes?";
- 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 outcomes".

B.3. Evidence Review: Bronchiectasis and Severe COVID-19 Outcomes

B.3.a. Strength & Direction of Evidence

Table 2. Evidence Examined for Associations Between Bronchiectasis and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Overall, the evidence[1-3] is inconsistent on an association between bronchiectasis and mortality. All three studies were found to have a moderate threat to internal validity. • Strength of Association: Measures of association range from 0.38 to an unadjusted value of 1.93. • Precision of Association: Confidence intervals are wide in one study[3] and crossed the null in two studies[1, 3]. • Consistency of Association: Results were inconsistent across studies. • Applicability of Association: Each study was conducted outside of the United States in countries including England, China, and Turkey. Summary of Evidence: • Two cohort studies[1, 3] (N = 8,257,389) reported an increase in the risk of mortality and underlying bronchiectasis. ▪ One cohort study[1] of adults in England (N = 8,256,161) reported an increase in the adjusted hazard of mortality for the 41,271 people with underlying bronchiectasis. This association persisted whether adjusted for age and sex [aHR: 1.35 (95% CI 1.14 – 1.60), p = NR]; age, sex, and other demographic factors [aHR: 1.29 (95% CI: 1.09 – 1.52), p = NR]; or age, sex, demographic factors, and comorbidities [aHR: 1.12 (95% CI: 0.94 – 1.33), p = NR]. When the hazard ratio was adjusted for all possible confounders, confidence intervals crossed the null, reducing confidence in the measure of association. ▪ One cohort study[3] in Turkey (N = 1,228) reported a univariable analysis of 12 patients, one of whom died, suggesting an increase in the risk of mortality for COVID-19 for hospitalized patients with COVID-19 [OR: 1.93 (0.25–15.21); p = 0.53]. The sample size and number of events were small which contributed to wide confidence intervals that crossed the null, resulting in limited confidence in these results. • One cohort study[2] of hospitalized patients in China (N = 39,420), reported a multivariable analysis that adjusted for age, sex, and other underlying comorbidities. Results suggested a decrease in the adjusted odds of mortality for the 313 patients with underlying bronchiectasis [aOR: 0.38 (95%CI: 0.21 - 0.70); p < 0.01].
ICU admission	Evidence from two studies[1, 2] suggests a non-statistically significant increase in the risk of ICU admission with the presence of underlying bronchiectasis. Both studies were found to have a moderate threat to internal validity. • Strength of Association: Adjusted measures of association range from 1.26 to 1.47. • Precision of Association: Confidence intervals were not wide but crossed the null in both studies. • Consistency of Association: Results were consistent across studies. • Applicability of Association: Settings and populations were applicable. • Two cohort studies[1, 2] reported increases in the adjusted hazard or odds of ICU admission with underlying bronchiectasis; however, confidence intervals crossed the null, reducing the confidence in these findings.

	▪ One cohort study[1] of adults in England (N = 8,256,161) reported an increase in the adjusted hazard of ICU admission for people with underlying bronchiectasis. This association persisted whether adjusted for age and sex [aHR: 1.36 (95% CI: 0.85 – 2.17), p = NR]; age, sex, and other demographic factors [aHR: 1.46 (95% CI: 0.91 – 2.33), p = NR]; or age, sex, demographic factors, and comorbidities [aHR: 1.47 (95%CI: 0.91 – 2.36), p = NR]. However, the number of patients with this exposure and outcome was small (n = 18), which likely contributed to confidence intervals that crossed the null in each of these analyses, reducing our confidence in the measure of association. ▪ One cohort study[2] of hospitalized patients in China (N = 39,420), reported a multivariable analysis that adjusted for age, sex, and other underlying comorbidities. Results suggested an increase in the adjusted odds of ICU admission for people with underlying bronchiectasis [aOR: 1.25 (95% CI: 0.89-1.75), p = 0.20]. However, confidence intervals crossed the null reducing confidence in these results
Intubation	Limited evidence from one study[2] suggests a decrease in the risk of intubation the presence of underlying bronchiectasis. Aggregation indices are not calculated for outcomes with only one supporting study which was found to have moderate threat to internal validity. ▪ One cohort study[2] of hospitalized patients in China (N = 39,420) reported a multivariable analysis that adjusted for age, sex, and other underlying comorbidities. Results suggested a protective effect for underlying bronchiectasis and a decrease in the adjusted odds of intubation for these patients [aOR: 0.69 (95% CI: 0.39 - 1.24); p = 0.22]. However, confidence intervals cross the null, reducing confidence in the measure of effect.
Hospitalization	Limited evidence from one study[1] suggests an increased in the risk of hospitalization with the presence of underlying bronchiectasis. Aggregation indices are not calculated for outcomes with only one supporting study which was found to have moderate threat to internal validity. ▪ One cohort study[1] of adults in England (N = 8,256,161) reported an increase in the adjusted hazard of hospitalization for patients with underlying bronchiectasis. This association persisted whether adjusted for age and sex [aHR: 1.70 (95% CI: 1.52 – 1.90), p = NR]; age, sex, and other demographic factors [aHR: 1.67 (95% CI: 1.49 – 1.87), p = NR]; or age, sex, demographic factors, and comorbidities [aHR: 1.34 (95% CI: 1.20– 1.50), p = NR].

B.3.b. Extracted Evidence

Table 3. Extracted Studies Reporting the Association Between Bronchiectasis and Severe COVID-19 Outcomes

Author: Aveyard[1] **Year:** 2021 **Data Extractor:** TR **Reviewer:** DOS **Study design:** Retrospective cohort study **Study Objective:** To assess whether chronic lung disease or use of inhaled corticosteroids (ICS) affects the risk of contracting severe COVID-19. **Internal Validity Assessments (IVA) Score:** 24 (moderate)	**Population:** N= 8,256,161 **Setting:** 1,205 general practices **Location:** England, UK **Study dates:** January 24, 2020 –April 30, 2020 **Inclusion criteria:** All patients aged 20 years and older registered with one of the 1,205 general practices in England contributing to the Research database (version 44, uploaded March 23, 2020) were included in this population cohort study. Data were linked to Public Health England's database of SARS-CoV-2 testing and English hospital admissions, ICU admissions, and deaths for COVID-19. **Exclusion criteria:** NR	**Health Condition Category:** Chronic lung disease, Multiple comorbid conditions **Medical Condition, n/N (%):** Bronchiectasis: 41271/ 8,256,161 (0.5%) **Control/Comparison group, n/N (%):** Bronchiectasis: 8,214,890/8,256,161 (99.5%)	**Medical Condition(s):** *Bronchiectasis:* ND **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR Inhaled corticosteroids (ICS): commonly used treatments for airways disease **Outcome Definitions:** *Mortality:* confirmed or suspected COVID-19 (ICD-10 codes U07.1 and U07.2) on the death certificate, including deaths in and out of hospital *ICU admission: a*dmission to an ICU with severe COVID-19 (ICD-10 code U07.1 or U07.2) in Intensive Care National Audit and Research Centre (ICNARC) records *Intubation:* NR *Ventilation:* NR *Hospitalization:* positive test for SARS-CoV-2 and appearing in the Hospital Episode Statistics dataset as an in-patient within 30 days of that test or having an International Classification of Diseases (ICD)-10 code U07.1 for confirmed COVID-19 or U07.2 for suspected COVID-19 *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *aHR: Adjusted Hazard Ratio for all other respiratory diseases, ethnicity, socioeconomic status, region of England, body-mass index, smoking status, non-smoking-related illness (hypertension, type 1 diabetes, chronic liver disease, chronic neurological disease) and smoking-related illness (coronary heart disease, stroke, atrial fibrillation, type 2 diabetes, chronic kidney disease)* *HR: Hazard Ratio* *Mortality, n/N (%):* Bronchiectasis: • aHR: 1.12 (95% CI: 0.94-1.33) • HR: 4.77 (95% CI: 4.03-5.65) • Bronchiectasis: 138/41,271 (0.3%) *ICU admission, n/N (%):* Bronchiectasis: • aHR: 1.47 (95% CI: 0.91-2.36) • HR: 2.37 (95% CI: 1.49-3.78) • Bronchiectasis: 18/41,271 (<0.1%) *Hospitalization, n/N (%):* Bronchiectasis: • aHR: 1.34 (95% CI: 1.20-1.50) • HR: 4.53 (95% CI: 4.06-5.07) • Bronchiectasis: 319/41,271 (0.8%) **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** *Mortality:* ICS: • aHR: 1.15 (95% CI: 1.01-1.31) • HR: 2.63 (95% CI: 2.44-2.84) *ICU admission:* ICS: • aHR: 1.63 (95% CI: 1.18-2.24)

				• HR: 2.10 (95% CI: 1.78-2.46) *Hospitalization:* ICS: • aHR: 1.13 (95% CI: 1.03-1.23) • HR: 2.72 (95% CI: 2.60-2.85) **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Guan [2] **Year:** 2021 **Data Extractor:** DOS **Reviewer:** MW **Study design:** Retrospective cohort **Study Objective:** To explore the association between chronic respiratory diseases (CRD) and the clinical outcomes of COVID-19. **IVA Score:** 24 (moderate)	**Population:** N = 39,420 **Setting:** National COVID-19 reporting system **Location:** China **Study dates:** December 2019 - May 6, 2020 **Inclusion criteria:** All hospitalized patients had to have a diagnosis of laboratory-confirmed COVID-19. All patients had established Chronic Respiratory Disease (CRD) before admission. Data derived from platform of in-patient Electronic Medical Records (EMR) authorized by National Health Commission. Since the initial outbreak, submission of EMR from individual hospitals designated for admitting patients with COVID-19 was requested by the National health Commission. **Exclusion criteria:** Patients without any information on comorbidities, clinical outcomes, age or sex data,	**Health Condition Category:** Chronic lung disease, Multiple comorbid conditions **Medical Condition, n/N (%):** Bronchiectasis: 313/39,420 (0.8%) **Control/Comparison group, n/N (%):** No bronchiectasis: 39,107/39,420 (99.2%)	**Medical Condition(s):** *Bronchiectasis:* physician diagnosis (radiological with or without clinical bronchiectasis) at hospital admission or discharge from hospital was extracted with computer software based on ICD-10 codes from EMR; all diagnoses made based on either history documents in clinical charts or the clinical manifestations consisted with global guidelines **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* death within 30 days after hospitalization *ICU admission:* admission to the intensive care unit *Intubation:* NR *Ventilation:* noninvasive ventilation, invasive mechanical ventilation, ECMO *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *aOR: Adjusted odds ratio; multivariable logistic regression adjusting for age, sex, and other systemic comorbidities* *OR: Odds ratio; univariable logistic regression* *Mortality, n/N (%):* • Bronchiectasis: • aOR: 0.38 (95% CI: 0.21-0.70), p=0.02 • OR: 0.66 (95% CI: 0.36-1.21) • Bronchiectasis: 11/313 (3.5%) • No bronchiectasis: 2042/39107 (5.2%) *ICU admission, n/N (%):* Bronchiectasis: • aOR: 1.25 (95% CI: 0.89-1.75), p=0.196 • OR: 1.50 (95% CI: 1.07-2.09) • Bronchiectasis: 40/313 (12.8%) • No bronchiectasis: 3479/39107 (8.9%) *Invasive ventilation, n/N (%):* Bronchiectasis: • aOR: 0.69 (95% CI: 0.39-1.24), p=0.217 • OR: 1.00 (95% CI: 0.56-1.78) • Bronchiectasis: 12/313 (3.8%) • No bronchiectasis: 1501/39107 (3.8%)

	discharge records, or admission date.			**Severity of Condition**: NR **Duration of Condition**: NR **Treatment/ Associated Therapy**: NR **Comorbid Conditions**: *Mortality, n/N (%):* COPD & bronchiectasis: • aOR: 0.66 (95% CI: 0.2-2.22), p=0.505 • OR: 1.71 (95% CI: 0.52-5.59) • COPD & asthma: 3/35 (8.6%) • No COPD & asthma: 2050/39385 (5.2%) Asthma & bronchiectasis: • aOR: 0.94 (95% CI: 0.11-7.75), p=0.95 • OR: 1.82 (95% CI: 0.23-14.22) • COPD & asthma: 1/11 (9.1%) • No COPD & asthma: 2052/39409 (5.2%) *ICU admission, n/N (%):* COPD & bronchiectasis: • aOR: 1.2 (95% CI: 0.46-3.11), p=0.706 • OR: 1.70 (95% CI: 0.66-4.38) • COPD & asthma: 5/35 (14.3%) • No COPD & asthma: 3514/39385 (8.9%) Asthma & bronchiectasis: • aOR: 0.81 (95% CI: 0.1-6.36), p=0.839 • OR: 1.02 (95% CI: 0.13-7.97) • COPD & asthma: 1/11 (9.1%) • No COPD & asthma: 3518/39409 (8.9%) *Invasive ventilation, n/N (%):* COPD & bronchiectasis: • aOR: 0.38 (95% CI: 0.05-2.75), p=0.335 • OR: 0.74 (95% CI: 0.10-5.41) • COPD & asthma: 1/35 (2.9%) • No COPD & asthma: 1512/39385 (3.8%) Asthma & bronchiectasis: • aOR: 0 (95% CI: 0-0), p=0.946

				• OR: 0 (95% CI: 0-0) • COPD & asthma: 0/11 (0%) • No COPD & asthma: 1513/39409 (3.8%) **Risk Markers**: NR **Long-term Sequelae:** NR
Author: Kokturk[3] **Year:** 2021 **Data Extractor:** MW **Reviewer:** DOS **Study Design:** Retrospective cohort **Study Objective:** To evaluate the clinical outcomes of hospitalized patients and to predict COVID-19 mortality among highly suspected patients. **IVA Score:** 24 (Moderate)	**Population:** N=1500 **Setting:** 26 Centers (17 university hospitals, 2 large tertiary hospitals, 2 secondary care hospitals and 5 private hospitals) **Location:** Turkey **Study dates:** March 11 – July 18, 2020 **Inclusion criteria:** Patients admitted to the hospital during study dates with a proven presence of a positive nucleic acid amplification test or a positive rapid antigen detection test together with clinical and radiographic findings that were strongly suggestive of COVID-19, and Highly probable cases presented with similar clinical and radiographic findings but could not be confirmed with an RT-PCR test. **Exclusion criteria:** NR	**Health Condition Category:** Chronic Lung Disease **Medical Condition, n/N (%):** Bronchiectasis: 12/1500 (0.8%) **Control/Comparison group, n/N (%):** No bronchiectasis: 1488/1500 (99.2%)	**Medical Condition(s):** *Bronchiectasis:* ND **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *OR: Odds ratio; univariable logistic regression* *Mortality, n/N (%):* Bronchiectasis: • OR: 1.93 (95% CI: 0.25–15.21), p=0.531 • Non-survivors: 1/67 (1.5%) • Survivors: 11/1433 (0.8%) **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR

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

Table 4. Internal Validity Assessments (IVA) of Extracted Studies Reporting the Association Between Bronchiectasis and Severe COVID-19 Outcomes

	Author Year	Aveyard 2021[1]	Guan 2021[2]	Kokturk 2021[3]
	Outcome	Mortality, ICU, hospitalization	Mortality, ICU admission, ventilation	Mortality
Domain	**Signaling question**	Data from medical records	Data from EMR	Data from 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	1	1	1
Selection Bias: Sampling	Randomization appropriately performed	0	0	0
	Allocation adequately concealed	0	0	0
	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	0	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	0	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	1
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	24	24
	Low, Moderate, High	Moderate	Moderate	Moderate

B. References

1. Aveyard P, Gao M, Lindson N, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *The Lancet Respiratory Medicine*. 2021;9(8):909-923. doi:10.1016/S2213-2600(21)00095-3
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C. 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
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
ECMO	extracorporeal membrane oxygenation
EMR	electronic medical records
ERT	evidence review team
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
ND	not defined

NR	not reviewed
OR	odds ratio
PECO	population, exposure, comparator, and outcomes
RT-PCR	real time polymerase chain reaction