Brief Summary of Findings on the Association Between Cystic Fibrosis and Severe COVID-19 Outcomes

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Summary of Finding

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A. Methods

The aim of this review is to identify and synthesize the best available evidence on the association between cystic fibrosis and severe COVID-19 to update the Centers for Disease Control and Prevention (CDC) website on underlying conditions and enable the creation of a provider-specific website with more rigorous information.

The methods for underlying conditions and risk factors are outlined on the webpage, https://www.cdc.gov/coronavirus/2019-ncov/science/sciencebriefs/systematic-review-process.html.

These methods were established in May 2021 and are used for conditions and risk factors where CDC conducted the review. Below are methodologic highlights and additional methods unique to this review. For more information, please visit https://www.cdc.gov/coronavirus/2019- ncov/science/science-briefs/systematic-review-process.html.

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, outcome (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 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 if they reported exposures and outcomes relevant to this review.

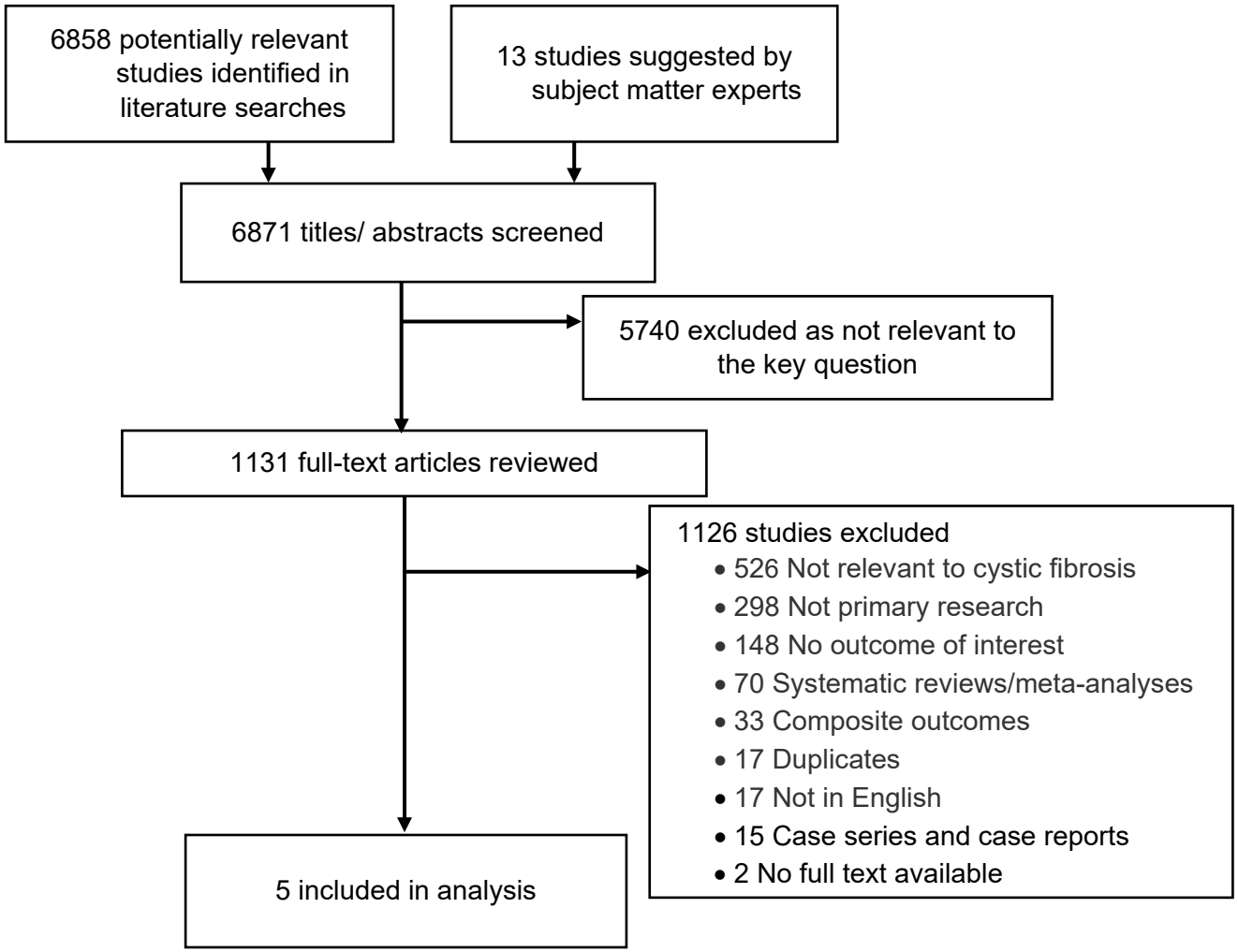
A.2. Study Selection

Titles and abstracts from references were screened by dual reviewers (C.N.S., J.K.K., C.O., D.O.S., T.R., M.C., E.C.S., J.H., 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 screened by two independent reviewers, and disagreements were resolved by discussion (C.N.S., J.K.K., D.O.S., M.C., 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. Internal Validity Assessment

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. The denominators used in the aggregation tables are of people diagnosed with COVID-19. If the number was not given, the denominator was listed as “not reported” (NR).

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 December 3, 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 PECO question "What is the association between chronic lung disease 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 relevant to the PECO question "what is the association between cystic fibrosis and severe COVID-19?";
- were not available as full-text;
- were a systematic review or meta-analysis;
- were a conference abstract, poster, letter to the editor, or reply letter;
- examined solely lung transplant, cancer, or immunocompromised populations;
- reported autopsy results; and
- reported only composite outcome measures for "severe COVID-19".

B.3. Evidence Review: Cystic Fibrosis and Severe COVID-19

B.3.a. Strength & Direction of Evidence

Table 2. Evidence Examined for Associations with Cystic Fibrosis and Severe COVID-19

Note: For studies with a significant likelihood of overlapping populations in the same age range[1,2], the results of only one of these studies was included in qualitative aggregations for each outcome measure. Evidence on pediatric patients is reported as a sub-analysis[3], despite the possible overlap of study

populations[1,2,4,5]. If multiple studies with overlapping populations reported the same outcome, the study with the largest denominator was included for that analysis.

Outcome	Results
Mortality	Evidence from four studies[1,3-5] (N = 1,759) is inconclusive on the association between underlying cystic fibrosis (CF) and mortality in people with COVID-19. All four studies were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 1.83. • Precision of Association: One study reported wide confidence intervals that crossed the null. • Consistency of Association: The evidence is inconsistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence • One study[4] (N = 826 including patients with CF and propensity score matched patients) reported an effect measure suggesting that CF is associated with an increase in mortality among people with COVID-19. ▪ One cohort study[4] (N = 826) of COVID-19 patients in the U.S. reported an increase in the risk of mortality among COVID-19 patients with CF when compared to propensity score matched COVID-19 patients without CF [RR: 1.83 (95%CI: 0.92-3.66), p=NR]. Patients were 1:1 propensity score-matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender. This study included patients with and without solid organ transplants. The use of ICD-10 coding to identify patients with CF has not been validated and could contribute to misclassification bias. This study also reported a wide confidence interval that crossed the null, decreasing confidence in the findings. • Two international studies[1,5] (N = 828[1]) examining similar populations reported ratios and proportions suggesting that CF is associated with lower mortality among people with COVID-19. For both studies, people with CF were identified through the European Cystic Fibrosis Society Patient Registry. ▪ One cohort study[5] (N = 130) of CF patients of all ages compared mortality for people with CF and COVID-19 to the general population with COVID-19. This paper reported a lower percentage of people with CF and COVID-19 died than in the general population with COVID-19, however, this difference did not reach statistical significance [3.85% (NR/NR) vs. 7.46% (NR/NR), p = 0.13]. Authors updated this study, examining a longer period of time and additional patients[1] (N=828). In this study, the proportion of people with CF and COVID-19 who died decreased [1.4% (11/812)]. No comparison was made to the general population. • One international study[3] (N = 105) reported on the prevalence of mortality in children with underlying CF and COVID-19. ▪ One international cohort study[3] (N = 105) reported no deaths among children with underlying CF and COVID-19. This study may have patients overlapped with the children reported in other studies[1,5] as it included patients from the Cystic Fibrosis Registry Global Harmonization Group, a collaborative international group of patient registries.

ICU Admission	Evidence from four studies[1,3-5] (N = 1,759[1,3,4]) suggests that underlying CF is associated with an increase in ICU admission in people with COVID-19. All four studies were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 1.78. • Precision of Association: One study reported a wide confidence interval that did not cross the null. • Consistency of Association: Overall, the evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Three studies[1,4,5] (N = 1,654[1,4]) reported that CF is associated with an increase in ICU admission. ▪ One cohort study[4] (N = 826 including both patients with CF and propensity score matched patients) of COVID-19 patients in the U.S., reported an increase in the risk of ICU admission among patients with CF when compared to propensity score matched patients without CF [RR: 1.78 (95%CI: 1.13-2.79), p=NR]. Patients were 1:1 propensity score matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender. The use of ICD-10 coding to identify patients with CF has not been validated and could contribute to misclassification bias. This study also reported a wide confidence interval. ▪ One international cohort study[5] (N = 130) of CF patients of all ages compared ICU admission for people with CF and COVID-19 to the general population with COVID-19. This paper reported a significantly higher percentage of people with cystic fibrosis were admitted to the ICU when compared to the general population [10.1% (12/119) vs. 3.1% (15,860/508,098), p < 0.01]. Authors updated this study, examining a longer period of time and additional patients[1] (N=828). In this study, the proportion of people with CF and COVID-19 who were admitted to the ICU decreased [2.5% (21/826)]. No comparison was made to the general population. People with CF were identified through the European Cystic Fibrosis Society Patient Registry. • One international study[3] (N = 105) reported on the prevalence of ICU admission in patients with underlying CF and COVID-19. ▪ One international cohort study[3] (N = 105) reported that 1.2% (1/83) of pediatric patients with underlying CF and COVID-19 were admitted to the ICU. This study may have patients overlapped with the children reported in other studies[1,4,5] as it included patients from the Cystic Fibrosis Registry Global Harmonization Group, a collaborative international group of patient registries.
Intubation	Limited descriptive evidence from three studies[1,3,5] (N = 933[1,3]) is inconclusive on an association between underlying cystic fibrosis and intubation (invasive ventilation and ECMO) in people with COVID-19. All three were found to have a moderate threat to internal validity. • Strength of Association: No measures of association were reported. • Precision of Association: Confidence intervals were not reported. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable.

	Summary of Evidence • Three international studies[1,3,5] (N = 933[1,3]) reported the prevalence of intubation in people with underlying CF and COVID-19. ▪ One international cohort study[3] (N = 105) reported that 5.0% (1/20) of hospitalized patients with underlying CF and COVID-19 were invasively ventilated. This study may have patients overlapped with the children reported in other studies[1,5] as it included patients from the Cystic Fibrosis Registry Global Harmonization Group, a collaborative international group of patient registries. The number of reported cases of intubation are small. ▪ One international cohort study[5] (N = 130) of people with CF of all ages reported that 6.3% (5/80) of patients with underlying CF and COVID-19 were invasively ventilated and 2.5% (2/80) required ECMO. Authors updated this study, examining a longer period of time and additional patients[1] (N=828). In this study, the proportion of people with CF and COVID-19 who were invasively ventilated [1.5% (12/820)] and put on ECMO [0.5% (4/757)] decreased. No comparison was made to the general population for patients in this study.
Ventilation	Evidence from four studies[1,3-5] (N = 1,759[1,3,4]) is inconclusive on the association between underlying cystic fibrosis and ventilation in people with COVID-19. All four studies were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 1.53. • Precision of Association: One study reported wide confidence intervals that crossed the null. • Consistency of Association: The evidence is inconsistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • One study[4] (N = 826 including both patients with CF and propensity score matched patients) reported an effect measure suggesting that CF is associated with an increase in mechanical ventilation among people with COVID-19. ▪ One cohort study[4] (N = 826) of COVID-19 patients in the U.S. reported an increase in the risk of mechanical ventilation among patients with CF compared to propensity score matched patients without CF [RR: 1.53 (95%CI: 0.84-2.78), p=NR]. Patients were 1:1 propensity score matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender. The use of ICD-10 coding to identify patients with CF has not been validated and could contribute to misclassification bias. This study also reported a wide confidence interval that crossed the null, decreasing confidence in the findings. • Three international studies[1,3,5] (N = 933[1,3]) reported the prevalence of non-invasive ventilation for people with CF and COVID-19. ▪ One international cohort study[5] (N = 130) of CF patients of all ages reported that 6.3% (5/80) of patients with underlying CF and COVID-19 were non-invasively ventilated. Authors updated this study, examining a longer period of time and additional patients[1] (N=828). In this study, the proportion of people with CF and

	COVID-19 who were non-invasively ventilated by BIPAP or CPAP [1.9% (16/821)] or high-flow nasal canula oxygen therapy [1.4% (5/353)] decreased. No comparison was made. ▪ One international cohort study[3] (N = 105) reported that 10% (2/20) of patients with CF and COVID-19 were non-invasively ventilated. This study may have patients overlapped with the children reported in other studies[1,5]. The number of reported ventilations is small.
Hospitalization	Evidence from four studies[1,3-5] (N = 1,759[1,3,4]) suggests an increase in hospitalization in people with CF and COVID-19. All four studies were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 1.56. • Precision of Association: One study reported wide confidence intervals that do not cross the null. • Consistency of Association: The evidence is inconclusive. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Three studies[1,4,5] (N = 1,654[1,4]) reported that CF is associated with an increase in hospitalization. ▪ One cohort study[4] (N = 826 including both patients with CF and propensity score matched patients) of COVID-19 patients in the U.S., reported an increase in the risk of hospitalization among patients with CF when compared to propensity score matched patients without CF [RR: 1.56 (95%CI: 1.20-2.04), p=NR]. Patients were 1:1 propensity score matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender. The use of ICD-10 coding to identify patients with CF has not been validated and could contribute to misclassification bias. This study also reported a wide confidence interval that crossed the null, decreasing confidence in the findings. ▪ One international cohort study[5] (N = 130) of CF patients of all ages reported a significantly higher percentage of people with CF and COVID-19 were hospitalized compared to people with COVID-19 only [60.2% (71/118) vs. 25.7% (145,250/565,695), p<0.01]. Authors updated this study, examining a longer period of time and additional patients[1] (N=828). In this study, the proportion of people with CF and COVID-19 who were hospitalized decreased [23.7% (195/824)]. No comparison was made to the general population. • One international study[3] (N = 105) reported the prevalence of hospitalization for people with CF and COVID-19. ▪ One international cohort study[3] (N = 105) reported that 29.3% (24/82) of patients with underlying CF and COVID-19 were hospitalized. This study may have patients overlapped with the children reported in another study[1,4,5]. The number of reported hospitalizations is small.

Table 3. The Association Between Severity of Cystic Fibrosis and Severe COVID-19 Outcomes Including ICU Admission, Ventilation, & Hospitalization

Outcome	**Results**

ICU Admission	Evidence from two studies[1,2] (N = 1,009) suggests that increasing severity of CF may be associated with an increase in ICU admissions in patients with underlying CF and COVID-19. Both studies[1,2] were found to have a moderate threat to internal validity. • Strength of Association: One study reported adjusted effect measures ranging from 2.4 to 5.4. • Precision of Association: One study reported wide confidence intervals, some of which included the null. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence • Two cohort studies[1,2] (N = 1,009) reported data on different severity measures and ICU admission in CF patients with COVID-19. ▪ One international cohort study[1] (N = 828) of cystic fibrosis patients with COVID-19 conducted univariable analyses for multiple markers of severity in patients with CF and COVID-19 and reported data indicating or suggesting an increase in the odds of ICU admission was associated with CF related diabetes (CFRD) [OR 4.6 (95% CI: 2.3-9.5), p < 0.001], allergic bronchopulmonary aspergillosis (ABPA) [OR 1.8 (95% CI: 0.6-6.1), p < 0.50]; pancreatic insufficiency [OR 2.3 (95% CI: 0.5-10.8), p < 0.49], lung function ppFEV$_1$ ≤40% [OR 2.6 (95% CI: 0.7-9.7), p < 0.39], lung function ppFEV$_1$ 40-70% [OR 2.3 (95% CI: 1.1-5.1), p = 0.14], and coinfections such as *Burkholderia cepacia* complex [OR 1.8 (95% CI: 0.2-17.1), p < 0.72], methicillin-resistant *Staphylococcus aureus* (MRSA) [OR 2.5 (95% CI: 0.6-10.2), p < 0.40], *Stenotrophomonas maltophilia* [OR 1.3 (95% CI: 0.3-5.0), p < 0.73], and *Achromobacter* species [OR 2.3 (95% CI: 0.7-8.3), p < 0.40]. No association was reported between CF coinfections and ICU admission in patients with CF and coinfections including *Pseudomonas aeruginosa* [OR 1.0 (95% CI: 0.5-2.3), p = 0.90]. This study also reported data suggesting a decrease in ICU admission in CF patients with *Staphylococcus aureus* [OR 0.6 (95% CI: 0.2-1.4), p = 0.40] and *Aspergillus* colonization [OR 0.4 (95% CI: 0.0-3.5), p < 0.061]. This study had wide confidence intervals that included the null, decreasing confidence in the findings. ▪ One international cohort study[2] (N = 181) of CF patients with COVID-19 reported rates of ICU admission for different severity measures in CF patients with and without solid organ transplants. A higher proportion of people with CF-related diabetes (CFRD) were admitted to the ICU, regardless of having undergone a transplant [35.3% (6/17) vs. 14.3% (1/7)] or having no history of transplant [4.5% (1/22) vs. 3.7% (3/82)]. There was no proportional relationship between best FEV$_1$ and admission to the ICU, regardless of history of transplant. This study may have patients overlapped with patients reported in another study[1]. Samples sizes and number of ICU admissions are small, decreasing confidence in these results.
Ventilation	Limited evidence from one study[2] (N = 181) is insufficient to determine if there is an association between CFRD and underlying CF and ventilation. Aggregation indices cannot be measured for only one study. This study was found to have a moderate threat to internal validity.

	Summary of Evidence • One international study[2] (N = 181) reported data suggesting CFRD in COVID-19 patients is associated with ventilation. ▪ One international cohort study[2] (N=181) of cystic fibrosis patients with COVID-19 reported a higher proportion of people with CFRD and no history of organ transplant were ventilated compared to people without CFRD and no history of organ transplant [4.5% (1/22) vs. 2.5% (2/79), p = NR]. Samples sizes and number of ventilations are small, decreasing confidence in these results.
Hospitalization	Evidence from three studies[1-3] (N = 1,114) suggests increasing severity of CF may be associated with an increase in hospitalization for COVID-19 patients. All three studies[1-3] were found to have a moderate threat to internal validity. • Strength of Association: One study reported adjusted effect measures ranging from 1.2 to 5.4. • Precision of Association: One study reported wide confidence intervals, some of which included the null. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Three international cohort studies[1-3] (N = 1,114) reported data on different severity measures and hospitalization in CF patients with COVID-19. ▪ One international cohort study[1] (N = 828) of cystic fibrosis patients with COVID-19 examined the association between hospitalization and several measures of severity for CF patients with COVID-19. This study reported adjusted effect measures indicating an increase in the odds of hospitalization is associated with decreasing ppFEV1 (lung function $ppFEV_1$ ≤40% [aOR 5.4 (95% CI: 2.2-13.0), p < 0.001]; $ppFEV_1$ 40-70% [aOR 2.4 (95% CI: 1.6-3.6), p < 0.001]). This study also reported an increase in the adjusted odds of hospitalization was associated with CFRD [aOR 1.7 (95% CI: 1.1-2.6), p < 0.03], pancreatic insufficiency (aOR 1.2 (95% CI: 0.8-1.8), p = 0.40), and *Pseudomonas aeruginosa* coinfection [aOR 1.2 (95% CI: 0.7-1.9), p < 0.49] when adjusting for gender, age, genotype, BMI, lung function, pancreatic enzymes, CFRD, lung transplant, CFTR modulator therapy, azithromycin, or *Pseudomonas aeruginosa* coinfection. ▪ This study also conducted univariable analyses for multiple markers of severity in patients with CF and COVID-19 and reported data indicating or suggesting an increase in the odds of hospitalization was associated with ABPA [OR 2.5 (95% CI: 1.5-4.2), p < 0.001], and coinfections including MRSA [OR 1.5 (95% CI: 0.9-2.6), p = 0.19], Achromobacter species [OR 2.3 (95% CI: 1.5-3.6), p < 0.001], *Stenotrophomonas maltophilia* [OR 1.6 (95% CI: 1.0-2.5), p = 0.07], and colonization with Aspergillus species [OR 1.9 (95% CI: 1.0-3.5), p < 0.7]. This study reported data suggesting no difference in hospitalization in CF patients with *Burkholderia cepacia* complex [OR 1.0 (95% CI: 0.4-2.4), p < 0.94], and *Staphylococcus aureus* coinfections [OR 0.8 (95% CI: 0.6-1.1), p = 0.18].

	▪ This study had wide confidence intervals that included the null, decreasing confidence in the findings. ▪ One international cohort study[2] (N=181) of cystic fibrosis patients of all ages with COVID-19, reported on severity measures and hospitalizations in people with CF and COVID-19. A higher proportion of hospital admissions was reported for people with CFRD than without CFRD regardless of a history of solid organ transplant [78.9% (15/19) vs. 71.4% (5/7); p = NR], or no solid organ transplant [55.6% (20/36) vs. 48.1% (39/81); p=0.46]. A higher proportion of patients with best FEV_1<70 were hospitalized regardless of history of transplant [87.5% (7/8) vs. 66.7% (8/12); p = NR], or no history of transplant [70.0% (42/60) vs. 27.5% (19/69); p < 0.01]. This difference reached statistical significance in patients with no history of transplant. This study may have patients overlapped with patients reported in another study[1]. ▪ One international cohort study[3] (N=105) of children whose population overlapped with the population of two studies[1,2] reported a higher proportion of patients with CFRD were hospitalized [55.6% (5/9) vs. 26.0% (19/73); p=0.116]. Additionally, a significantly higher proportion of children with best FEV_1<70 were hospitalized [66.7% (10/15)] vs. 22.0% (11/50); p < 0.01]. Lastly, this international study of children with cystic fibrosis reported a significantly higher proportion of people with pancreatic insufficiency were hospitalized [33.8% (24/71) vs. 0% (0/11); p = 0.023]. This study reported a low number of hospitalizations.

Table 4. The Association Between Biomarkers of Cystic Fibrosis and Severe COVID-19 Outcomes Including ICU Admission and Hospitalization

Outcome	Results
ICU Admission	Limited evidence from two studies[1,2] (N = 1,009) is insufficient to determine an association between biomarkers and ICU admission for COVID-19 patients with underlying CF. Both studies[1,2] were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 1.8. • Precision of Association: One study reported a wide confidence interval. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Two international studies[1,2] (N = 1,009) reported data on biomarkers for underlying CF and ICU admission in CF patients with COVID-19. ▪ One international study[1] (N=828) of people with cystic fibrosis and COVID-19 reported an increase in the unadjusted odds of ICU admissions in patients with any F508del genotype compared to patients without any F508del genotype [OR 1.8 (95% CI: 1.1-3.2), p = 0.14]. This study had a wide confidence interval. ▪ One international cohort study[2] (N = 181) reported data on the presence of heterozygous and homozygous F508del genotypes. The proportion of ICU admission was higher in patients with homozygous F508del

	genotypes than those with heterozygous F508del genotypes for patients with no history of transplant [7.0% (3/52) vs. 2.0% (1/51)], and higher for heterozygous F508del for patients with a history of transplant [19.0% (3/16) vs. 33.0% (3/8)]. The number of ICU admissions were small, and statistical analyses were not conducted, reducing confidence in these findings.
Hospitalization	Limited evidence from three studies[1-3] (N = 1,114) suggests no association between biomarkers and hospitalization for COVID-19 patients with underlying CF. All three studies[1-3] were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 0.9. • Precision of Association: One study reported a wide confidence interval that included the null. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence • Three international studies[1-3] (N = 1,114) reported data on biomarkers and hospitalization in CF patients with COVID-19. ▪ One international cohort study[1] (N=828) of people with cystic fibrosis and COVID-19 reported no difference in hospitalizations in patients with any F508del genotype compared to patients without any F508del genotype when adjusting for gender, age, BMI, lung function, pancreatic enzymes, CFRD, lung transplant, CFTR modulator therapy, azithromycin, and Pseudomonas aeruginosa [aOR 0.9 (95% CI: 0.6-1.3), p = 0.47]. This study had a wide confidence interval that included the null, decreasing confidence in the findings. ▪ One international cohort study[3] (N=105) of children with cystic fibrosis reported no difference in the proportion of specific genetic mutations among hospitalized and non-hospitalized children for homozygous F508del mutation (22.0% vs 78.0%; p = 0.22) and heterozygous F508del (30.0% vs. 70.0%; p > 0.99), however the sample size was small, and it is probable that this population overlaps with the population in two studies[1,2]. ▪ One international cohort study[2] (N=181) of people with cystic fibrosis reported on the presence of heterozygous and homozygous F508del genotypes. The proportion of hospitalization was lower in patients with homozygous F508del genotypes than those with heterozygous F508ded genotypes for patients with no history of transplant [43.0% (16/37) vs. 53.0% (27/51)], and the same in people with a history of transplant [75.0% (12/16) vs. 75.0% (6/8)]. However, the number of hospitalizations were small and statistical analyses were not conducted, reducing confidence in these findings.

Table 5. The Association Between Treatments for People with Cystic Fibrosis and Severe COVID-19 Outcomes including ICU Admission and Hospitalization

Outcome	Results
ICU Admission	Limited evidence from one study[1] (N = 828) is insufficient to determine if there is an association between treatments for underlying CF and ICU admission. Aggregation indices cannot be measured for only one study. This study was found to have a moderate threat to internal validity.

	Summary of Evidence: • One international study[1] (N = 828) reported data on treatments for underlying CF and ICU admission in patients with COVID-19. ▪ One international cohort study[1] (N = 828) of patients with CF and COVID-19 reported unadjusted effect measures suggesting an increase in ICU admissions with the use of inhaled antibiotics [OR 5.5 (95% CI: 1.2-25.0), p = 0.14], oral antibiotics [OR 3.7 (95% CI: 1.3-10.5), p = 0.14], and azithromycin [OR 2.0 (95% CI: 1.0-4.1), p < 0.17]. This study also reported unadjusted effect measures suggesting a decrease in ICU admission with the use of CFTR modulator therapy [OR 0.5 (95% CI: 0.2-1.2), p = 0.31], inhaled steroid [OR 0.5 (95% CI: 0.2-1.0), p < 0.17], DNase [OR 0.6 (95% CI: 0.2-1.6), p < 0.50], and hypertonic saline [OR 0.8 (95% CI: 0.3-2.4), p < 0.73]. This study had wide confidence intervals that included the null, decreasing our confidence in the findings.
Hospitalization	Evidence from three studies[1,3,4] (N = 1,759) indicates that CFTR modulator therapy is associated with a decrease in hospitalization among COVID-19 patients with underlying CF. Limited data from one study[1] is insufficient to determine if there is an association between other treatments for underlying CF and hospitalization. All three studies were found to have a moderate threat to internal validity. • Strength of Association: Two studies reported adjusted measures of association ranging from of 0.57-1.8. • Precision of Association: Two studies reported wide confidence intervals that cross the null. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Three studies[1,3,4] (N = 1,759) reported data suggesting that CFTR modulator therapy is associated with a decrease in hospitalization in COVID-19 patients with underlying CF. ▪ One international cohort study[1] (N = 828) of COVID-19 patients with CF reported a decrease in the adjusted odds of hospitalization among patients with CF undergoing CFTR modulator therapy [aOR 0.6 (95% CI: 0.4-1.0), p = 0.05] when adjusting for gender, age, genotype, BMI, lung function, pancreatic enzymes, CFRD, lung transplant, CFTR modulator therapy, azithromycin, and *Pseudomonas aeruginosa* coinfection. This study also conducted univariable analyses and reported no difference in the unadjusted odds of hospitalization among patients with CF using DNase [OR 1.1 (95% CI: 0.7-2.0), p < 0.75] or hypertonic saline [OR 0.9 (95% CI: 0.5-1.6), p = 0.88]. This study reported data indicating or suggesting an increase in the adjusted odds of hospitalization among patients with CF using Azithromycin treatment for a coinfection [aOR 1.8 (95% CI: 1.1-2.9), p < 0.02] when adjusting for gender, age, genotype, BMI, lung function, pancreatic enzymes, CFRD, lung transplant, CFTR modulator therapy, azithromycin, and *Pseudomonas aeruginosa* coinfection. This study also reported data suggesting an increase in the unadjusted odds of hospitalization among patients with CF using inhaled antibiotics [OR 1.9 (95% CI: 1.1-3.5), p < 0.05], oral

	antibiotics [OR 1.5 (95% CI: 1.1-2.1), p < 0.04], and inhaled steroids [OR 1.4 (95% CI: 0.9-2.2), p = 0.19]. This study had wide confidence intervals that included the null, decreasing confidence in the findings. ▪ One cohort study[4] (N = 826 including both patients with CF and propensity score matched patients) of COVID-19 patients in the U.S. reported data suggesting a decrease in the unadjusted odds of hospitalization among CF patients using CFTR potentiator agent when compared to patients not using CFTR potentiator agent [OR: 0.57 (95% CI: 0.30-1.08), p = NR]. The use of ICD-10 coding to identify patients with CF has not been validated and could contribute to misclassification bias. This study also reported a wide confidence interval that crossed the null, decreasing confidence in the findings. ▪ One international cohort study[3] (N=106) of children with cystic fibrosis reported on CFTR modulator therapy among children with CF and COVID-19 who were and were not hospitalized. The proportion of those not on modulator therapy was significantly higher among hospitalized children than those who were not hospitalized (p < 0.01). It is probable that the population overlaps with populations from two other studies[1,4].

Table 6. The Association Between Cystic Fibrosis and Other Comorbidities and Severe COVID-19 Outcomes including ICU Admission and Hospitalization

ICU Admission	**Evidence from one study[1] (N = 828) is insufficient to determine if there is an association between comorbidities and underlying CF and ICU admission. Aggregation indices cannot be measured for only one study. This study was found to have a moderate threat to internal validity.** **Summary of Evidence:** • **One cohort study[1] (N = 828) reported data on underlying CF, other comorbidities, and ICU admission in patients with COVID-19.** ▪ **One international study[1] (N = 828) reported unadjusted effect measures suggesting low BMI (underweight), chronic liver disease, and systemic arterial hypertension are associated with an increase in ICU admissions among COVID-19 patients with underlying CF [low BMI (underweight): OR 1.5 (95% CI: 0.5-4.8), p < 0.69; chronic liver disease: OR 1.3 (95% CI: 0.5-3.5), p < 0.72; systemic arterial hypertension: OR 5.5 (95% CI: 1.1-27.0), p = 0.14]. This study did not define CF and had wide confidence intervals that included the null, decreasing our confidence in the findings.**
Hospitalization	Evidence from one study[1] (N = 828) is insufficient to determine if there is an association between comorbidities and underlying CF and hospitalization. Aggregation indices cannot be measured for only one study. This study was found to have a moderate threat to internal validity. Summary of Evidence: • One cohort study[1] (N = 828) reported data on underlying CF, other comorbidities, and hospitalization in patients with COVID-19.

	▪ One international study[1] (N = 828) examined multiple comorbidities and risk factors for an association with hospitalization among patients with CF and COVID-19. This study reported data suggesting an increase in the adjusted odds of hospitalization was associated with low BMI (underweight) [aOR 1.9 (95% CI: 0.8-4.5), p < 0.12] when controlling for gender, age, genotype, lung function, pancreatic enzymes, CFRD, lung transplant, CFTR modulator therapy, azithromycin, and *Pseudomonas aeruginosa*. This study also conducted univariable analyses and reported effect measures indicating systemic arterial hypertension is associated with an increase in the unadjusted odds of hospitalizations among COVID-19 patients with underlying CF [OR 3.1 (95% CI: 1.8-5.4), p < 0.001], and no difference in the unadjusted odds of hospitalization in CF patients with chronic liver disease [OR 1.1 (95% CI: 0.9-1.5), p < 0.46]. This study had wide confidence intervals that included the null, decreasing confidence in the findings.

Table 7. The Association Between Cystic Fibrosis and Transplants and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Evidence from two studies[1,2] (N = 1,009) suggests that lung and other solid organ transplants are associated with increased mortality in patients with underlying CF and COVID-19. Both studies[1,2] were found to have a moderate threat to internal validity. • Strength of Association: No measures of association were reported. • Precision of Association: No confidence intervals were reported. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence • Two international studies[1,2] (N = 1,009) reported an increase in mortality in CF patients with COVID-19 and organ transplants. ▪ One international cohort study[1] (N = 828) of CF patients with COVID-19 reported a higher death rate for patients with lung transplants than for those without lung transplants [5.4% (4/74) vs 0.9% (7/738), p = NR]. Lung transplants may improve lung function but could also cause patients to become immunocompromised. This may increase the risk of mortality. This study did not conduct statistical analyses. ▪ One international cohort study[2] (N = 181) of CF patients with COVID-19 reported a higher death rate for people with cystic fibrosis and prior organ transplants than for those with CF but no organ transplants [9.4 % (3/32) vs. 2.7% (4/149), p = NR]. Organ transplants may cause patients to become immunocompromised, which may increase the risk of mortality. One death among the non-transplanted cases was reported to be due to underlying CF, not COVID-19. Among those who had not received a solid organ transplant, all had FEV_1<70 (2 had FEV_1<40, 2 had FEV_1=40-70) and 75% (3/4) had cystic fibrosis-related diabetes (CFRD). This

	study may have patients overlapped with patients reported in another study[1]. Sample sizes were small and statistical analyses were not conducted.
ICU Admission	Evidence from two studies[1,2] (N = 1,009) suggests that lung transplants are associated with increased ICU admission in patients with CF and COVID-19. Both studies[1,2] were found to have a moderate threat to internal validity. • Strength of Association: One study reported a measure of association of 6.5. • Precision of Association: One study reported wide confidence intervals. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Two studies[1,2] (N = 1,009) reported data on underlying CF, transplants, and ICU admission in patients with COVID-19. ▪ One international study[1] (N = 828) reported an unadjusted effect measure suggesting lung transplants are associated with an increase in ICU admissions among COVID-19 patients with underlying CF [OR 6.5 (95% CI: 3.2-13.2), p < 0.001]. Lung transplants may improve lung function but could also cause patients to become immunocompromised. This may increase the risk of ICU admissions. This study had wide confidence intervals that included the null, decreasing our confidence in the findings. ▪ One international cohort study[2] (N = 181) of CF patients with COVID-19 reported a higher proportion of people with CF and a history of solid organ transplant were admitted to the ICU compared with those with CF who had no history of transplants [25% (7/28)] vs. 3.6% (4/110)]. Organ transplants may cause patients to become immunocompromised, which may increase the risk of ICU admissions. This study may have patients overlapped with patients reported in another study[1]. Samples sizes and number of ICU admissions are small, decreasing confidence in these results.
Intubation	Evidence from one study[1] (N = 828) is insufficient to determine if there is an association between lung transplants and underlying CF and intubation. Aggregation indices cannot be measured for only one study. This study was found to be at moderate threat to internal validity. Summary of Evidence • One cohort study[1] (N = 828) reported data suggesting that lung transplant in COVID-19 patients with CF is associated with increased intubation. ▪ One international cohort study[1] (N = 828) of cystic fibrosis patients with COVID-19 reported an increase in invasive ventilation [7.7% (6/78) vs 0.8% (6/742), p = NR] and ECMO [2.7% (2/74) vs 0.3% (2/683) among patients with lung transplants when compared to those without lung transplants. Lung transplants may improve lung function but could also cause patients to become immunocompromised. This may increase

	the risk of intubations. This study reported a low number of intubations, decreasing confidence in the result.
Ventilation	Evidence from two studies[1,2] (N = 1,009) suggests that lung and organ transplant is associated with ventilation in patients with underlying CF and COVID-19. Both studies were found to have a moderate threat to internal validity. • Strength of Association: No measures of association were reported. • Precision of Association: No confidence intervals were reported. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence • Two cohort studies[1,2] (N = 1,009) reported data suggesting that lung transplant in COVID-19 patients with CF is associated with increased ventilation. ▪ One international cohort study[1] (N = 828) of cystic fibrosis patients with COVID-19 reported an increase in BIPAP/CPAP among patients with lung transplants when compared to those without lung transplants [3.8% (3/78) vs 2.7% (13/743). This study reported a decrease in high-flow nasal canula oxygen therapy among patients with lung transplants when compared to those without lung transplants [0% (0/19) vs 1.5% (5/334)]. Lung transplants may improve lung function but could also cause patients to become immunocompromised. This may increase the risk of ventilation. This study reported a low number of ventilation, decreasing confidence in the results. ▪ One international cohort study[2] (N=181) of cystic fibrosis patients with COVID-19 reported a higher proportion of people with CF and a history of organ transplant were ventilated compared with those with CF who had no history of transplants [17.4% (4/23)] vs. 3.0% (3/101), p = NR]. Organ transplants may cause patients to become immunocompromised, which may increase the risk of ventilation. This study may have patients overlapped with patients reported in another study[1]. Samples sizes and number of ventilations are small, decreasing confidence in these results.
Hospitalization	Evidence from two studies[1,2] (N = 1,009) suggests that lung or solid organ transplants are associated with increased hospitalization in patients with CF and COVID-19. Both studies[1,2] were found to have a moderate threat to internal validity. • Strength of Association: One study reported an adjusted measure of association of3.2. • Precision of Association: One study reported wide confidence intervals. • Consistency of Association: The evidence is consistent. • Applicability of Association: Populations and settings were applicable. Summary of Evidence: • Two cohort studies[1,2] (N = 1,009) reported data on underlying CF, transplants, and hospitalization in patients with COVID-19.

	▪ One international cohort study[1] (N = 828) reported that an increase in the adjusted odds of hospitalization was associated with lung transplant [aOR 3.2 (95% CI: 1.7-6.1), p < 0.001] when controlling for gender, age, genotype, lung function, pancreatic enzymes, CFRD, CFTR modulator therapy, azithromycin, and *Pseudomonas aeruginosa*. Lung transplants may improve lung function but could also cause patients to become immunocompromised. This may increase the risk of hospitalization. This study had wide confidence intervals that included the null, decreasing confidence in the findings. ▪ One international cohort study[2] (N=181) of cystic fibrosis patients of all ages with COVID-19, reported a significantly higher proportion of hospital admissions was reported for people with a history of transplants compared to people with no history of transplant [74.1% (20/27) vs. 46.8% (66/141); p < 0.01]. Organ transplants may cause patients to become immunocompromised, which may increase the risk of hospitalization. This study may have patients overlapped with patients reported in another study[1].

Table 8. The Association Between Cystic Fibrosis and Risk Markers and Severe COVID-19 Outcomes including ICU Admission and Hospitalization

Outcome	Results
ICU Admission	Limited evidence from one study[1] (N = 828) is insufficient to determine if there is an association between underlying CF, risk markers, and ICU admission. Aggregation indices cannot be measured for only one study. This study was found to have a moderate threat to internal validity. Summary of Evidence: • One international study[1] (N = 828) reported data on underlying CF, risk markers, and ICU admission in patients with COVID-19. ▪ One international cohort study[1] (N = 828) reported effect measures suggesting male sex (compared to female sex) and increasing age (compared to 0-17 years old) were associated with an increase in the unadjusted odds of ICU admission among COVID-19 patients with underlying CF [18-29: OR 0.7 (95% CI: 0.2-2.0), p < 0.68; 30-39: OR 1.5 (95% CI: 0.4-5.8), p < 0.69; ≥40: OR 2.9 (95% CI: 0.9-9.1), p = 0.20; male: OR 1.2 (95% CI: 0.6-2.3), p < 0.72]. This study had wide confidence intervals that included the null, decreasing our confidence in the findings.
Hospitalization	Limited evidence from one study[1] (N = 828) is insufficient to determine if there is an association between underlying CF, risk markers, and hospitalization. Aggregation indices cannot be measured for only one study. This study was found to have a moderate threat to internal validity. Summary of Evidence: • One international study[1] (N = 828) reported data on underlying CF, risk markers, and hospitalization in patients with COVID-19.

	▪ One international cohort study[1] (N = 828) reported a measure of association suggesting that older age (compared to 0-17 years old) is associated with an increase in the adjusted odds of hospitalization [≥40: aOR 1.3 (95% CI: 0.7-2.2), p < 0.43] when holding gender, age, genotype, BMI, lung function, pancreatic enzymes, CFRD, lung transplant, CFTR modulator therapy, azithromycin, and *Pseudomonas aeruginosa* coinfection constant. This study also reported effect measures suggesting male sex (compared to female sex) and ages 18-39 (compared to 0-17 years old) could be associated with a decrease in the adjusted odds of hospitalization among COVID-19 patients with underlying CF [male: aOR 0.8 (95% CI: 0.5-1.2), p = 0.24; 18-29: aOR 0.6 (95% CI: 0.4-1.0), p < 0.06; 30-39: aOR 0.8 (95% CI: 0.4-1.7), p < 0.61]. This study had wide confidence intervals that included the null, decreasing our confidence in the findings.

B.3.b. Extracted Evidence

Table 9 Extracted Studies Reporting the Association between Cystic Fibrosis and Severe COVID-19 Outcomes

Study	Population and Setting	Exposure	Definitions	Results
Author: Aveyard **Year: 2021** **Data Extractor: TR** **Reviewer: DOS** **Study design: Cohort** **Study Objective: To assess whether chronic lung disease or use of inhaled corticosteroids (ICS) affects the risk of contracting severe COVID-19** **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 QResearch 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	**Health Condition Category:** Chronic Lung Disease, Risk Factors, Multiple Comorbid Conditions, Cancer **Medical Condition, n/N (%):** COPD: 193,520/ 8,256,161 (2.3%) Asthma: 1,090,028/ 8,256,161 (13.2%) Bronchiectasis: 41271/ 8,256,161 (0.5%) Cystic fibrosis: 2081/ 8,256,161 (<1%) Sarcoidosis: 17624/ 8,256,161 (0.2%) Extrinsic allergic alveolitis: 2331/ 8,256,161 (<1%) Idiopathic pulmonary fibrosis: 7454/ 8,256,161 (0.1%) Other interstitial lung diseases: 5677/ 8,256,161 (0.1%) Lung cancer: 10792/ 8,256,161 (0.1%) **Control/Comparison group, n/N (%):** COPD: 8,062,641/ 8,256,161 (97.7%) Asthma: 7,166,133/ 8,256,161 (86.6%) Bronchiectasis: 8,214,890/ 8,256,161 (99.5%) Cystic fibrosis: 8,254,080/ 8,256,161 (99.9%) Sarcoidosis: 8,238,537/8,256,161 (99.8%) Extrinsic allergic alveolitis: 8,253,830/ 8,256,161 (99.9%)	**Medical Condition(s):** *COPD:* ND *Asthma:* ND *Bronchiectasis:* ND *Cystic fibrosis:* ND *Sarcoidosis:* ND *Extrinsic allergic alveolitis:* ND *Idiopathic pulmonary fibrosis:* ND *Other interstitial lung diseases:* ND *Lung cancer:* ND **Severity Measure(s):** *Active asthma:* having at least one prescription for asthma medication *Severe asthma:* being prescribed at least three different classes of medication for asthma in the year before cohort entry **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	**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 (%):* COPD: • aHR: 1.54 (95%CI: 1.42-1.67) • HR: 6.66 (95%CI: 6.19-7.18) • COPD: 811/193,520 (0.4%) Asthma: • aHR: 0.99 (95%CI: 0.91-1.07) • HR: 0.96 (95%CI: 0.89-1.04) • Asthma: 762/1,090,028 (0.1%) Cystic fibrosis: • Cystic fibrosis: 0/2081 (0%) Bronchiectasis: • aHR: 1.12 (95%CI: 0.94-1.33) • HR: 4.77 (95%CI: 4.03-5.65)

	Exclusion criteria: NR	Idiopathic pulmonary fibrosis: 8,248,707/ 8,256,161 (99.9%) Other interstitial lung diseases: 8,250,484/ 8,256,161 (99.9%) Lung cancer: 8,245,369/ 8,256,161 (99.9%)	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	• Bronchiectasis: 138/41,271 (0.3%) Sarcoidosis: • aHR: 1.41 (95%CI: 0.99-1.99) • HR: 2.53 (95%CI: 1.79-3.58) • Sarcoidosis: 32/17,624 (0.2%) Extrinsic allergic alveolitis: • aHR: 1.56 (95%CI: 0.78-3.13) • HR: 4.82 (95%CI: 2.41-9.65) • Extrinsic allergic alveolitis: 8/2,331 (0.3%) Idiopathic pulmonary fibrosis: • aHR: 1.47 (95%CI: 1.12-1.92) • HR: 12.09 (95%CI: 9.42-15.53) • Idiopathic pulmonary fibrosis: 62/7,454 (0.8%) Other interstitial lung diseases: • aHR: 2.05 (95%CI: 1.49-2.81) • HR: 11.37 (95%CI: 8.48-15.25) • Other interstitial lung diseases: 45/5,677 (0.8%) Lung cancer: • aHR: 1.77 (95%CI: 1.37-2.29) • HR: 8.33 (95%CI: 6.46-10.74) • Lung cancer: 60/10,792 (0.6%) *ICU admission, n/N (%):* COPD: • aHR: 0.89 (95%CI: 0.68-1.17) • HR: 1.68 (95%CI: 1.29-2.18) • COPD: 59/193,520 (<0.1%) Asthma: • aHR: 1.08 (95%CI: 0.93-1.25) • HR: 1.05 (95%CI: 0.91-1.22) • 213/1,090,028 (<0.1%) 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%) Sarcoidosis: • aHR: 1.51 (95%CI: 0.81-2.81) • HR: 3.06 (95%CI: 1.64-5.70) • Sarcoidosis: 10/17,624 (0.1%) Idiopathic pulmonary fibrosis:

				• aHR: 1.97 (95%CI: 0.85-4.55) • HR: 4.48 (95%CI: 2.01-9.99) • Idiopathic pulmonary fibrosis: 6/7,454 (0.1%) *Hospitalization, n/N (%):* • COPD: • aHR: 1.54 (95%CI: 1.45-1.63) • HR: 5.09 (95%CI: 4.83-5.36) • COPD: 1,555/193,520 (0.8%) Asthma: • aHR: 1.18 (95%CI: 1.13-1.24) • HR: 1.22 (95%CI: 1.17-1.28) • Asthma: 2,266/1,090,028 (0.2%) Cystic fibrosis: • aHR: 1.55 (95%CI: 0.65-3.73) • HR: 1.37 (95%CI: 0.57-3.30) • Cystic fibrosis: 5/2,081 (0.2%) 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%) Sarcoidosis: • aHR: 1.36 (95%CI: 1.10-1.68) • HR: 2.74 (95%CI: 2.21-3.39) • Sarcoidosis: 84/17,624 (0.5%) Extrinsic allergic alveolitis: • aHR: 1.35 (95%CI: 0.82-2.21) • HR: 3.97 (95%CI: 2.43-6.48) • Extrinsic allergic alveolitis: 16/2,331 (0.7%) Idiopathic pulmonary fibrosis: • aHR: 1.59 (95%CI: 1.30-1.95) • HR: 8.80 (95%CI: 7.29-10.62) • Idiopathic pulmonary fibrosis: 110/7,454 (1.5%) Other interstitial lung diseases: • aHR: 1.66 (95%CI: 1.30-2.12) • HR: 7.57 (95%CI: 6.02-9.53) • Other interstitial lung diseases: 73/5,677 (1.3%) **Severity of Condition:** *Mortality, n/N (%):* Active asthma:

				• aHR: 1.05 (95%CI: 0.96-1.15) • HR: 1.62 (95%CI: 1.49-1.77) • Active asthma: 602/535,126 (0.1%) Severe asthma: • aHR: 1.08 (95%CI: 0.98-1.19) • HR: 1.78 (95%CI: 1.62-1.95) • Severe asthma: 476/385,702 (0.1%) *ICU admission, n/N (%):* Active asthma: • aHR: 1.34 (95%CI: 1.14-1.58) • HR: 1.73 (95%CI: 1.47-2.03) • Active asthma: 165/535,126 (<0.1%) Severe asthma: • aHR: 1.30 (95%CI: 1.08-1.58) • HR: 1.79 (95%CI: 1.49-2.15) • Severe asthma: 124/385,702 (<0.1%) *Hospitalization, n/N (%):* Active asthma: • aHR: 1.26 (95%CI: 1.20-1.33) • HR: 1.95 (95%CI: 1.85-2.05) • Active asthma: 1,720/535,126 (0.3%) Severe asthma: • aHR: 1.29 (95%CI: 1.22-1.37) • HR: 2.14 (95%CI: 2.02-2.26) • Severe asthma: 1,369/385,702 (0.4%) **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:** *Mortality among COPD patients, n/N (%):* Age: p<0.001 40-59: • HR: 4.61 (95%CI: 2.93-7.26) • Died: 20/31,175 (0.06%) 60-79: • HR: 2.26 (95%CI: 1.99-2.57) • Died: 310/115,046 (0.30%) ≥ 80: • HR: 1.28 (95%CI: 1.16-1.42) • Died: 481/46,194 (1.04%) Sex: p=0.005 Women: • HR: 1.77 (95%CI: 1.56-2.00) • Died: 321/92,676 (0.35%) Men: • HR: 1.42 (95%CI: 1.28-1.57) • Died: 490/100,844 (0.49%) Ethnic group: p=0.009 White: • HR: 1.55 (95%CI: 1.41-1.69) • Died: 635/161,376 (0.39%) Asian: • HR: 1.01 (95%CI: 0.70-1.44) • Died: 33/4,463 (0.74%) Black: • HR: 1.10 (95%CI: 0.70-1.73) • Died: 20/1,900 (1.05%) Chinese: • HR: 0.68 (95%CI: 0.09-5.05) • Died: <5/178 (2.81%) Other or not recorded: • HR: 1.89 (95%CI: 1.56-2.29) • Died: 122/25,603 (0.48%)

				Smoking status: Non-smoker: p=0.360 • HR: 1.51 (95%CI: 1.27-1.79) • Died: 145/23,935 (0.61%) Ex-smoker: • HR: 1.52 (95%CI: 1.37-1.67) • Died: 547/104,638 (0.52%) Current smoker: • HR: 1.72 (95%CI: 1.37-2.14) • Died: 145/64,775 (0.22%) *ICU admission among COPD patients, n/N (%):* Age: p=0.466 40-59: • HR: 1.40 (95%CI: 0.69-2.83) • ICU admission: 8/31,175 (0.03%) 60-79: • HR: 0.90 (95%CI: 0.66-1.22) • ICU admission: 45/115,046 (0.04%) ≥ 80: • HR: 1.21 (95%CI: 0.51-2.85) • ICU admission: 6/46,194 (0.01%) Sex: p=0.025 Women: • HR: 1.43 (95%CI: 0.91-2.27) • ICU admission: 20/92,676 (0.02%) Men: • HR: 0.74 (95%CI: 0.53-1.04) • ICU admission: 39/100,844 (0.04%) Ethnic group: p=0.826 White: • HR: 0.91 (95%CI: 0.66-1.26) • ICU admission: 42/161,376 (0.03%) Asian: • HR: 0.74 (95%CI: 0.30-1.79) • ICU admission: 5/4,463 (0.11%) Black: • HR: 1.18 (95%CI: 0.44-3.20) • ICU admission: <5/1,900 (0.26%) Other or not recorded: • HR: 0.79 (95%CI: 0.38-1.54)

				• ICU admission: 8/25,603 (0.03%) Smoking status: p=0.732 Non-smoker: • HR: 0.76 (95%CI: 0.38-1.54) • ICU admission: 8/23,935 (0.03%) Ex-smoker: • HR: 0.89 (95%CI: 0.65-1.21) • ICU admission: 45/104,638 (0.04%) Current smoker: • HR: 1.18 (95%CI: 0.51-2.72) • ICU admission: 6/64,775 (0.01%) *Hospitalization among COPD patients, n/N (%):* Age: p<0.0001 40-59: • HR: 2.57 (95%CI: 2.08-3.17) • Hospitalized: 91/31,175 (0.29%) 60-79: • HR: 1.93 (95%CI: 1.78-2.09) • Hospitalized: 725/115,046 (0.63%) ≥ 80: • HR: 1.31 (95%CI: 1.21-1.42) • Hospitalized: 739/46,194 (1.60%) Sex: p=0.090 Women: • HR: 1.63 (95%CI: 1.50-1.78) • Hospitalized: 635/92,676 (0.69%) Men: • HR: 1.49 (95%CI: 1.38-1.60) • Hospitalized: 920/100,844 (0.91%) Ethnic group: p=0.0002 White: • HR: 1.55 (95%CI: 1.46-1.66) • Hospitalized: 1,223/161,376 (0.76%) Asian: • HR: 0.98 (95%CI: 0.76-1.27) • Hospitalized: 61/4,463 (1.4%) Black:

				• HR: 1.17 (95%CI: 0.85-1.61) • Hospitalized: 39/1,900 (2.10%) Chinese: • HR: 1.33 (95%CI: 0.33-5.45) • Hospitalized: <5/178 (2.81%) Other or not recorded: • HR: 1.83 (95%CI: 1.59-2.10) • Hospitalized: 230/25,603 (0.90%) Smoking status: p=0.0002 Non-smoker: • HR: 1.37 (95%CI: 1.21-1.56) • Hospitalized: 253/23,935 (1.06%) Ex-smoker: • HR: 1.51 (95%CI: 1.41-1.62) • Hospitalized:1,031/104,638 (0.99%) Current smoker: • HR: 1.94 (95%CI: 1.69-2.23) • Hospitalized: 265/64,775 (0.41%) *Mortality among asthma patients, n/N (%):* Age: p=0.001 20-39: • HR: 2.11 (95%CI: 1.00-4.42) • Died: 9/459,751 (<0.01%) 40-59: • HR: 1.27 (95%CI: 0.95-1.69) • Died: 54/352,853 (0.02%) 60-79: • HR: 1.09 (95%CI: 0.96-1.24) • Died: 275/218,881 (0.13%) ≥ 80: • HR: 0.85 (95%CI: 0.77-0.95) • Died: 424/58,543 (0.72%) Sex: p=0.628 Women: • HR: 0.97 (95%CI: 0.86-1.08) • Died: 362/571,497 (0.06%) Men: • HR: 1.01 (95%CI: 0.90-1.12) • Died: 400/518,531 (0.08%)

				Ethnic group: p=0.448 White: • HR: 0.96 (95%CI: 0.87-1.05) • Died: 514/84.083 (0.61%) Asian: • HR: 1.00 (95%CI: 0.78-1.27) • Died: 80/68,014 (0.12%) Black: • HR: 0.97 (95%CI: 0.72-1.32) • Died: 48/2,835 (1.69%) Chinese: • HR: 0.95 (95%CI: 0.22-4.03) • Died: <5/3,503 (0.14%) Other or not recorded: • HR: 1.14 (95%CI: 0.94-1.38) • Died: 118/206,076 (0.06%) Smoking status: p=0.396 Non-smoker: • HR: 0.99 (95%CI: 0.89-1.10) • Died: 374/624,797 (0.06%) Ex-smoker: • HR: 0.99 (95%CI: 0.88-1.11) • Died: 341/257,566 (0.13%) Current smoker: • HR: 0.91 (95%CI: 0.65-1.26) • Died: 40/193,373 (0.02%) *ICU admission among asthma patients, n/N (%):* Age: p=0.015 20-39: • HR: 2.16 (95%CI: 1.40-3.33) • ICU admission: 28/459,751 (0.01%) 40-59: • HR: 1.03 (95%CI: 0.81-1.30) • ICU admission: 78/352,853 (0.02%) 60-79: • HR: 1.03 (95%CI: 0.83-1.27) • ICU admission: 103/218,881 (0.05%) ≥ 80: • HR: 0.61 (95%CI: 0.22-1.69) • ICU admission: <5/58,543 (0.01%)

				Sex: p=0.021 Women: • HR: 1.36 (95%CI: 1.07-1.74) • ICU admission: 84/571,497 (0.01%) Men: • HR: 0.95 (95%CI: 0.79-1.15) • ICU admission: 129/518,531 (0.02%) Ethnic group: p=0.230 White: • HR: 1.18 (95%CI: 0.97-1.43) • ICU admission: 124/784,083 (0.02%) Asian: • HR: 0.94 (95%CI: 0.65-1.34) • ICU admission: 34/68,014 (0.05%) Black: • HR: 1.33 (95%CI: 0.88-2.02) • ICU admission: 26/28,352 (0.09%) Chinese: • HR: 0.99 (95%CI: 0.13-7.56) • ICU admission: <5/3,503 (0.14%) Other or not recorded: • HR: 0.77 (95%CI: 0.52-1.13) • ICU admission: 28/206,076 (0.01%) Smoking status: p=0.725 Non-smoker: • HR: 1.06 (95%CI: 0.88-1.28) • ICU admission: 124/624,797 (0.02%) Ex-smoker: • HR: 1.14 (95%CI: 0.90-1.45) • ICU admission: 81/257,566 (0.03%) Current smoker: • HR: 0.79 (95%CI: 0.36-1.73) • ICU admission: 7/193,373 (<0.01%) *Hospitalization among asthma patients, n/N (%):* Age: p<0.0001 20-39: • HR: 1.59 (95%CI: 1.37-1.86) • Hospitalized: 206/459,751 (0.04%) 40-59: • HR: 1.43 (95%CI: 1.29-1.57)

				• Hospitalized: 507/352,853 (0.14%) 60-79: • HR: 1.19 (95%CI: 1.10-1.28) • Hospitalized: 847/218,881 (0.39%) ≥ 80: • HR: 0.93 (95%CI: 0.86-1.00) • Hospitalized: 706/58,543 (1.21%) Sex: p=0.0001 Women: • HR: 1.29 (95%CI: 1.21-1.37) • Hospitalized: 1,238/571,497 (0.22%) Men: • HR: 1.08 (95%CI: 1.01-1.15) • Hospitalized: 1,028/518,531 (0.20%) Ethnic group: p=0.868 White: • HR: 1.20 (95%CI: 1.14-1.27) • Hospitalized: 1,539/748,083 (0.21%) Asian: • HR: 1.16 (95%CI: 1.01-1.33) • Hospitalized: 252/68,014 (0.37%) Black: • HR: 1.10 (95%CI: 0.93-1.31) • Hospitalized: 149/28,352 (0.53%) Chinese: • HR: 1.07 (95%CI: 0.43-2.67) • Hospitalized: 5/3,503 (0.14%) Other or not recorded: • HR: 1.15 (95%CI: 1.02-1.29) • Hospitalized: 321/206,076 (0.16%) Smoking status: p=0.286 Non-smoker: • HR: 1.18 (95%CI: 1.11-1.25) • Hospitalized: 1,205/624,797 (0.19%) Ex-smoker: • HR: 1.16 (95%CI: 1.07-1.25) • Hospitalized: 868/257,566 (0.34%) Current smoker: • HR: 1.32 (95%CI: 1.12-1.55) • Hospitalized: 182/193,373 (0.09%)

				Long-term Sequelae: NR
Author: Bain[3] **Year: 2021** **Data Extractor: CS** **Reviewer: DOS** **Study design: Cohort** **Study Objective: To report the clinical course and outcomes of SARS-CoV-2 infection in children with CF collated by an international collaborative group and representing the only large dataset thus far reported.** **IVA** **Score: 18 (moderate)**	**Population:** N=105 **Setting:** Collaborative international group of patient registries; Cystic Fibrosis Registry Global Harmonization Group **Location:** 13 out of 19 participating countries **Study dates:** February 1-August 7, 2020 **Inclusion criteria:** Children <18 years old with a confirmed diagnosis of cystic fibrosis (CF) and were either diagnosed with SARS-CoV-2 via PCR test on a respiratory sample or a clinical diagnosis was made in a hospital setting were included. **Exclusion criteria:** Cases reported via antibody testing alone or self-reporting were excluded.	**Health Condition Category:** Chronic Lung Disease, Risk Factors, Immunocompromised Status **Medical Condition, n/N (%):** Cystic fibrosis: 105/105 (100%) **Control/Comparison group, n/N (%):** N/A	**Medical Condition(s):** *Cystic fibrosis:* ND **Severity Measure(s):** *Pancreatic status:* insufficient or sufficient *CF related diabetes:* ND *Best percent predicted forced expiratory volume in one second (ppFEV$_1$):* median best ppFEV$_1$ within 12 months prior to infection for those over the age of five years **Clinical marker:** *Genotype:* Homozygous F508del or Heterozygous F508del **Treatment/ Associated Therapy:** *Cystic fibrosis transmembrane conductance regulator (CTFR) modulator therapy:* ND **Outcome Definitions:** *Mortality:* NR *ICU admission:* ND *Intubation:* NR *Ventilation:* non-invasive and invasive *Hospitalization:* ND *Non-elective readmissions*: NR **Comments:** none	**Severe COVID-19:** *ICU admission, n/N (%):* 1/83 (1%) *Invasive ventilation, n/N (%):* 1/20 (5%) *Non-invasive ventilation, n/N (%):* 2/20 (10%) *Hospitalization, n/N (%):* 24/82 (29%) **Severity of Condition:** *Hospitalization, n/N (%):* Pancreatic status: • Insufficient: 24/71 (34%) • Sufficient: 0/11 (0%) • p=0.029 CF related diabetes: • CF related diabetes: 5/9 (56%) • No CF related diabetes: 19/73 (26%) • p=0.116 Best ppFEV$_1$: • >70: 11/50 (22%) • 40-70: 8/12 (67%) • <40: 2/3 (67%) • p=0.002 **Clinical marker:** *Hospitalization, n/N (%):* Genotype: • Homozygous F508del: 8/36 (22%) • Heterozygous F508del: 7/23 (30%) • Other: 9/22 (41%) **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR *Hospitalization, n/N (%):* CTFR modulator therapy: • No modulator treatment: 14/30 (47%) • Modulator treatment: 6/40 (15%) • p=0.007 **Comorbid Conditions:** NR **Risk Markers:** *Hospitalization, n/N (%), or Median (IQR):* Sex:

				• Male: 12/44 (27%) • Female: 12/38 (32%) • p=0.808 Age: • 0-1 year: 2/9 (22%) • 2-4 years: 0/6 (0%) • 5-12 years: 7/29 (24%) • 13-18 years: 15/38 (39%) • p=0.099 Body mass index Z-score: • Male: -0.55 (-1.46 to -0.06) • Female: 0.32 (-0.55 to –0.92) • p=0.015 **Long-term Sequelae:** NR
Author: Beltramo **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 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**	**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 associated diagnoses by the ICD-10 codes U0710, U0711, U0712, U0714 or U0715, regardless of their age. Data obtained from t he national Programme de M edicalisation des Systemes d'Information (PMSI) database.	**Health Condition Category:** Chronic heart disease, Chronic lung disease, Cancer **Medical Condition, n/N (%):** Pulmonary hypertension: 341/89,530 (0.38%) Any CRD: 14351/89530 (16.0%) Chronic respiratory failure: 1433/89,530 (1.60%) Sleep apnea: 3581/89,530 (4.00%) Chronic obstructive pulmonary disease (COPD): 4866/89,530 (5.44%) Emphysema: 1426/89,530 (1.59%) Asthma: 3273/89,530 (3.66%) Cystic fibrosis (CF): 20/89,530 (0.02%) Interstitial lung disease (ILD): 1611/89,530 (1.80%) Pulmonary sarcoidosis: 159/89,530 (0.18%) Lung cancer: 977/89,530 (1.09%) **Control/Comparison group, n/N (%):** No CRD: 75179/89530 (84.0%)	**Medical Condition(s):** *Pulmonary hypertension*: ICD-10 I270 *Any CRD:* includes chronic respiratory failure, asthma, COPD, ILD, pulmonary hypertension, sarcoidosis, CF, and lung cancer *Chronic respiratory failure*: ICD-10 J961 *Sleep apnea*: ICD-10 G473 *COPD*: ICD-10 J40, J41, J42, J44 *Emphysema*: ICD-10 J43, J982 *Asthma*: ICD-10 J45, J46 *CF*: ICD-10 E840 *ILD*: ICD-10 J84 *Pulmonary sarcoidosis*: ICD-10 D86 *Lung cancer*: ICD-10 C34, C45 **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	**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 Any CRD: • Any CRD: 3363/14351 (23.43%) • No CRD: 11222/75179 (14.93%) • p<0.0001 Chronic respiratory failure: • aOR: 1.30 (95% CI: 1.06-1.59) • OR: 2.10 (95% CI: 1.74-2.54) • Chronic respiratory failure: 413/1433 (28.8%) • No CRD: 11222/75179 (14.93%) • p<0.05 Sleep apnea: • aOR: 0.95 (95% CI: 0.85-1.06) • OR: 1.12 (95% CI: 1.02-1.25) • Sleep apnea: 672/3581 (18.8%) • No CRD: 11222/75179 (14.93%)

IVA Score: 24 (moderate)	**Exclusion criteria:** NR		*Non-elective readmissions*: NR **Comments:** none	• p<0.05 COPD: • aOR: 1.14 (95% CI: 1.06-1.22) • OR: 1.72 (95% CI: 1.61-1.84) • COPD: 1229/4886 (25.3%) • No CRD: 11222/75179 (14.93%) • p<0.05 Emphysema: • aOR: 1.01 (95% CI: 0.83-1.22) • OR: 1.18 (95% CI: 0.99-1.42) • Emphysema: 312/1426 (21.8%) • No CRD: 11222/75179 (14.93%) Asthma: • aOR: 0.82 (95% CI: 0.71-0.94) • OR: 0.51 (95% CI: 0.45-0.58) • Asthma: 310/3273 (9.5%) • No CRD: 11222/75179 (14.93%) • p<0.05 Cystic fibrosis: • 0/20 (0.0%) ILD: • aOR: 1.20 (95% CI: 1.05-1.28) • OR: 1.41 (95% CI: 1.24-1.61) • ILD: 363/1611 (22.5%) • No CRD: 11222/75179 (14.93%) • p<0.05 Pulmonary sarcoidosis: • aOR: 2.11 (95% CI: 1.36-3.26) • OR: 1.38 (95% CI: 0.92-2.09) • Pulmonary sarcoidosis: 32/159 (20.1%) • No CRD: 11222/75179 (14.93%) Lung cancer: • aOR: 3.67 (95% CI: 3.20-4.21) • OR: 3.64 (95% CI: 3.20-4.14) • Lung cancer: 402/977 (41.2%) • 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 Any CRD: • Any CRD: 2985/14351 (20.80%) • No CRD: 12119/75179 (16.12%) • p<0.0001 Chronic respiratory failure: • aOR: 1.03 (95% CI: 0.81-1.30) • OR: 1.18 (95% CI: 0.94-1.49) • Chronic respiratory failure: 320/1433 (22.3%) • No CRD: 12119/75179 (16.12%) Sleep apnea: • aOR: 1.39 (95% CI: 1.27-1.53) • OR: 2.74 (95% CI: 2.52-2.98) • Sleep apnea: 1172/3581 (32.7%) • No CRD: 12119/75179 (16.12%) • p<0.05 COPD: • aOR: 1.16 (95% CI: 1.07-1.26) • OR: 1.47 (95% CI: 1.37-1.58) • COPD: 986/4866 (20.6%) • No CRD: 12119/75179 (16.12%) • p<0.05 Emphysema: • aOR: 1.83 (95% CI: 1.56-2.16) • OR: 2.09 (95% CI: 1.78-2.45) • Emphysema: 405/1426 (28.4%) • No CRD: 12119/75179 (16.12%) • p<0.05 Asthma: • aOR: 1.23 (95% CI: 1.12-1.36) • OR: 1.35 (95% CI: 1.23-1.48) • Asthma: 640/3273 (19.6%) • No CRD: 12119/75179 (16.12%) • p<0.05 Cystic fibrosis: • aOR: 0.60 (95% CI: 0.1-2.60) • OR: 0.63 (95% CI: 0.15-2.73) • Cystic fibrosis: 2/20 (10.0%) • No CRD: 12119/75179 (16.12%) ILD: • aOR: 2.42 (95% CI: 2.14-2.72) • OR: 2.77 (95% CI: 2.47-3.11)

				• ILD: 527/1611 (32.7%) • No CRD: 12119/75179 (16.12%) • p<0.05 Pulmonary sarcoidosis: • aOR: 2.65 (95% CI: 1.83-3.84) • OR: 2.94 (95% CI: 2.07-4.19) • Pulmonary sarcoidosis: 53/159 (33.3%) • No CRD: 12119/75179 (16.12%) • p<0.05 Lung cancer: • aOR: 0.77 (95% CI: 0.63-0.94) • OR: 0.78 (95% CI: 0.64-0.94) • Lung cancer: 117/977 (12.0%) • No CRD: 12119/75179 (16.12%) • p<0.05 **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR

Author: Hadi[4] **Year: 2021** **Data Extractor: CNS** **Reviewer: JKK** **Study Design: Cohort** **Study Objective: To report clinical outcomes in COVID-19 infection in a large cohort of people with cystic fibrosis (pwCF) and compare these outcomes to a propensity score matched cohort of people without CF.** **IVA Score: 24 (moderate)**	**Population:** N = 507,810 After matching N = 826 **Setting:** More than 40 health care organizations in research network TriNETX **Location:** U.S. **Study dates:** January 20, 2020-February 10, 2021 **Inclusion criteria:** Patients >16 years old with SARS-CoV-2 infection or COVID-19 diagnosis. Patients with cystic fibrosis were 1:1 propensity score matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender to patients without cystic fibrosis. **Exclusion criteria:** NR	**Population:** N = 507,810 After matching N = 826 **Setting:** More than 40 health care organizations in research network TriNETX **Location:** U.S. **Study dates:** January 20, 2020-February 10, 2021 **Inclusion criteria:** Patients >16 years old with SARS-CoV-2 infection or COVID-19 diagnosis. Patients with cystic fibrosis were 1:1 propensity score matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender to patients without cystic fibrosis. **Exclusion criteria:** NR	**Population:** N = 507,810 After matching N = 826 **Setting:** More than 40 health care organizations in research network TriNETX **Location:** U.S. **Study dates:** January 20, 2020-February 10, 2021 **Inclusion criteria:** Patients >16 years old with SARS-CoV-2 infection or COVID-19 diagnosis. Patients with cystic fibrosis were 1:1 propensity score matched by age, race, diabetes, hypertension, chronic lung diseases, chronic kidney disease, nicotine, dependence, heart failure, ischemic heart disease, body mass index, and gender to patients without cystic fibrosis. **Exclusion criteria:** NR	**Severe COVID-19:** *RR: Risk Ratio* *OR: Odds Ratio* After Propensity Score Matching: *Mortality, n/N (%):* • RR: 1.83 (95% CI: 0.92-3.66), p=NR • CF: 22/413 (5.33%) • No CF: 12/413 (2.91%) *ICU admission, n/N (%):* • RR: 1.78 (95% CI: 1.13-2.79), p=NR • CF: 48/413 (11.62%) • No CF: 27/413 (6.54%) *Mechanical ventilation, n/N (%):* • RR: 1.53 (95% CI: 0.84-2.78), p=NR • CF: 26/413 (6.30%) • No CF: 17/413 (4.12%) *Hospitalization, n/N (%):* • RR: 1.56 (95% CI: 1.20-2.04), p=NR • CF: 111/413 (26.88%) • No CF: 71/413 (17.19%) Before Propensity Score Matching: *Mortality, n/N (%):* • RR: 3.74 (95% CI: 2.02-4.57), p=NR • CF: 22/422 (5.21%) • No CF: 8,705/507,388 (1.72%) *ICU admission, n/N (%):* • RR: 4.55 (95% CI: 3.49-5.92), p=NR • CF: 49/422 (11.61%) • No CF: 12,953/507,388 (2.55%) *Mechanical ventilation, n/N (%):* • RR: 3.99 (95% CI: 2.75-5.79), p=NR • CF: 26/422 (6.16%) • No CF: 7,842/507,388 (1.55%) *Hospitalization, n/N (%):* • RR: 3.56 (95% CI: 3.05-4.16), p=NR • CF: 117/422 (27.73%)

				• No CF: 39,471/507,388 (7.78%) **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** *Hospitalization, n/N (%):* • OR: 0.57 (95% CI: 0.297-1.08), p=NR • CFTR potentiator agent user: 13/68 (19.12%) • No CFTR potentiator agent use: 104/353 (29.46%) **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Jung[1] **Year: 2021** **Data Extractor: CNS** **Reviewer: JKK** **Study design: Cohort study** **Study Objective: To expand the previously described cohort to include European pwCF who were diagnosed with SARS-CoV-2 infection up to December 31, 2020, to update SARS-CoV-2 incidence, and to provide the first large, detailed analysis of clinical presentation (including individual	**Population:** N= 828 **Setting:** Cystic fibrosis centers **Location:** 26 European countries (Armenia, Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Netherlands, North Macedonia, Norway, Poland, Portugal, Russia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, & United Kingdom) **Study dates:** February 1-December 31, 2020 **Inclusion criteria:** People with cystic fibrosis diagnosed with PCR-confirmed SARS-CoV-2 infection who were	**Medical Condition, n/N (%):** Cystic fibrosis: 828/828 (100%) **Control/Comparison group, n/N (%):** NR	**Medical Condition(s):** *Cystic fibrosis*: ND **Severity Measure(s):** *Lung-transplant status:* ND *Genotype:* Any F508del *Lung function:* (ppFEV$_1$) ≤40% (severe), >40-70% (moderate), or >70% (mild) *Pancreatic insufficiency:* ND *CF related diabetes:* ND *Allergic bronchopulmonary aspergillosis (ABPA):* ND *Pseudomonas aeruginosa:* ND *Staphylococcus aureus:* ND *Burkholderia cepacia complex:* ND *Methicillin-resistant Staphylococcus aureus (MRSA):* ND *Stenotrophomonas maltophilia:* ND *Achromobacter species:* ND *Aspergillus colonisation:* ND **Clinical marker:** NR **Treatment/ Associated Therapy, n/N (%):** *CFTR modulator therapy:* ND *Inhaled antibiotics:* ND	**Severe COVID-19:** *aOR: Adjusted odds ratio; mixed effects multivariable logistic regression adjusted for gender, age, genotype, BMI, lung function, pancreatic enzymes, CF related diabetes, lung transplant, CFTR modulator therapy, azithromycin and Pseudomonas aeruginosa* *OR: Odds ratio; mixed effects univariable logistic regression* *Mortality, case fatality rate:* • Cystic fibrosis: 11/812 (1.4%) *ICU admission, n/N (%):* Cystic fibrosis: 21/826 (2.5%) *Intubation, n/N (%):* *Invasive ventilation:* • Cystic fibrosis: 12/820 (1.5%) *ECMO:* • Cystic fibrosis: 4/757 (0.5%) *Ventilation, n/N (%):* *BIPAP or CPAP:* • Cystic fibrosis: 16/821 (1.9%) *High-flow nasal canula oxygen therapy:* • Cystic fibrosis: 5/353 (1.4%)

symptoms) and identification of risk factors associated with poorer outcomes. **IVA Score: 18 (moderate)**	reported by one of the 38 European Cystic Fibrosis Society Patient Registry member countries in 2018 (2017 for France). **Exclusion criteria:** Patients diagnosed by CT scan, serology, or antigen test without PCR confirmation.		*Oral antibiotics:* ND *Inhaled steroid:* ND *Azithromycin:* ND *DNase:* ND *Hypertonic saline:* ND **Outcome Definitions:** *Mortality:* ND *ICU admission:* ND *Intubation:* Invasive ventilation or ECMO *Ventilation*: BIPAP, CPAP, or high-flow nasal canula oxygen therapy *Hospitalization:* ND *Non-elective readmissions*: NR **Comments:** Reporting was voluntary, therefore cases may be under-reported with possible selection bias for more severe cases.	*Hospitalization, n/N (%)* • Cystic fibrosis: 195/824 (23.7%) **Severity of Condition:** *Mortality, n/N (%):* Lung-transplant status: • Lung transplant: 4/74 (5.4%) • Non-lung transplant: 7/738 (0.9%) *ICU admission, n/N (%):* Lung-transplant status: • OR: 6.5 (95% CI: 3.2-13.2), p<0.001 • Lung transplant: 8/78 (10.3%) • Non-lung transplant: 13/748 (1.7%) Genotype: • OR: 1.8 (95% CI: 1.1-3.2), p=0.144 Lung function: >40-70% • OR: 2.3 (95% CI: 1.1-5.1), p=0.144 ≤40% • OR: 2.6 (95% CI: 0.7-9.7), p=0.387 >70%: Ref Pancreatic insufficiency: • OR: 2.3 (95% CI: 0.5-10.8), p=0.487 CF related diabetes: • OR: 4.6 (95% CI: 2.3-9.5), p<0.001 ABPA: • OR: 1.8 (95% CI: 0.6-6.1), p=0.499 Pseudomonas aeruginosa: • OR: 1.0 (95% CI: 0.5-2.3), p=0.901 Staphylococcus aureus: • OR: 0.6 (95% CI: 0.2-1.4), p=0.401 Burkholderia cepacia complex: • OR: 1.8 (95% CI: 0.2-17.1), p=0.716 MRSA: • OR: 2.5 (95% CI: 0.6-10.2), p=0.396 Stenotrophomonas maltophilia: • OR: 1.3 (95% CI: 0.3-5.0), p=0.726 Achromobacter species: • OR: 2.3 (95% CI: 0.7-8.3), p=0.396 Aspergillus colonisation: • OR: 0.4 (95% CI: 0.0-3.5), p=0.607 *Intubation, n/N (%):* *Invasive ventilation:* Lung-transplant status:

				• Lung transplant: 6/78 (7.7%) • Non-lung transplant: 6/742 (0.8%) *ECMO:* Lung-transplant status: • Lung transplant: 2/74 (2.7%) • Non-lung transplant: 2/683 (0.3%) *Ventilation, n/N (%):* *BIPAP or CPAP:* Lung-transplant status: • Lung transplant: 3/78 (3.8%) • Non-lung transplant: 13/743 (2.7%) *High-flow nasal canula oxygen therapy:* Lung-transplant status: • Lung transplant: 0/19 (0%) • Non-lung transplant: 5/334 (1.5%) *Hospitalization, n/N (%):* Lung-transplant status: • aOR: 3.2 (95% CI: 1.7-6.1), p<0.001 • OR: 3.9 (95% CI: 2.8-5.4), p<0.001 • Lung transplant: 39/77 (50.6%) • Non-lung transplant: 156/747 (20.9%) Genotype: • aOR: 0.9 (95% CI: 0.6-1.3), p=0.472 • OR: 1.0 (95% CI: 0.7-1.3), p=0.905 Lung function: >40-70% • aOR: 2.4 (95% CI: 1.6-3.6), p<0.001 • OR: 2.7 (95% CI: 2.0-3.6), p<0.001 ≤40% • aOR: 5.4 (95% CI: 2.2-13.0), p<0.001 • OR: 8.1 (95% CI: 4.0-16.5), p<0.001 >70%: Ref Pancreatic insufficiency: • aOR: 1.2 (95% CI: 0.8-1.8), p=0.404 • OR: 1.8 (95% CI: 1.2-2.5), p=0.005 CF related diabetes: • aOR: 1.7 (95% CI: 1.1-2.6), p=0.027 • OR: 2.6 (95% CI: 1.9-3.7), p<0.001 ABPA: • OR: 2.5 (95% CI: 1.5-4.2), p<0.001 Pseudomonas aeruginosa: • aOR: 1.2 (95% CI: 0.7-1.9), p=0.485 • OR: 2.1 (95% CI: 1.5-3.0), p<0.001

				Staphylococcus aureus: • OR: 0.8 (95% CI: 0.6-1.1), p=0.180 Burkholderia cepacia complex: • OR: 1.0 (95% CI: 0.4-2.4), p=0.939 MRSA: • OR: 1.5 (95% CI: 0.9-2.6), p=0.191 Stenotrophomonas maltophilia: • OR: 1.6 (95% CI: 1.0-2.5), p=0.073 Achromobacter species: • OR: 2.3 (95% CI: 1.5-3.6), p<0.001 Aspergillus colonisation: • OR: 1.9 (95% CI: 1.0-3.5), p=0.068 **Duration of Condition:** NR **Treatment/ Associated Therapy:** *ICU admission, n/N (%):* CFTR modulator therapy: • OR: 0.5 (95% CI: 0.2-1.2), p=0.313 Inhaled antibiotics: • OR: 5.5 (95% CI: 1.2-25.0), p=0.144 Oral antibiotics: • OR: 3.7 (95% CI: 1.3-10.5), p=0.140 Inhaled steroid: • OR: 0.5 (95% CI: 0.2-1.0), p=0.165 Azithromycin: • OR: 2.0 (95% CI: 1.0-4.1), p=0.165 DNase: • OR: 0.6 (95% CI: 0.2-1.6), p=0.499 Hypertonic saline: • OR: 0.8 (95% CI: 0.3-2.4), p=0.726 *Hospitalization, n/N (%):* CFTR modulator therapy: • aOR: 0.6 (95% CI: 0.4-1.0), p=0.051 • OR: 0.7 (95% CI: 0.5-1.0), p=0.058 Inhaled antibiotics: • OR: 1.9 (95% CI: 1.1-3.5), p=0.049 Oral antibiotics: • OR: 1.5 (95% CI: 1.1-2.1), p=0.038 Inhaled steroid: • OR: 1.4 (95% CI: 0.9-2.2), p=0.191 Azithromycin: • aOR: 1.8 (95% CI: 1.1-2.9), p=0.017 • OR: 2.7 (95% CI: 1.9-3.8), p<0.001 DNase: • OR: 1.1 (95% CI: 0.7-2.0), p=0.747

				Hypertonic saline: • OR: 0.9 (95% CI: 0.5-1.6), p=0.883 **Comorbid Conditions:** *ICU admission, n/N (%):* BMI (underweight): • OR: 1.5 (95% CI: 0.5-4.8), p=0.685 Chronic liver GI disease: • OR: 1.3 (95% CI: 0.5-3.5), p=0.716 Systemic arterial hypertension: • OR: 5.5 (95% CI: 1.1-27.0), p=0.144 *Hospitalization, n/N (%):* BMI: • aOR: 1.9 (95% CI: 0.8-4.5), p=0.119 • OR: 3.8 (95% CI: 2.1-7.0), p<0.001 Chronic liver GI disease: • OR: 1.1 (95% CI: 0.9-1.5), p=0.459 Systemic arterial hypertension: • OR: 3.1 (95% CI: 1.8-5.4), p<0.001 **Risk Markers:** *ICU admission, n/N (%):* Gender (male): • OR: 1.2 (95% CI: 0.6-2.3), p=0.716 Age: 18-29 • OR: 0.7 (95% CI: 0.2-2.0), p=0.676 30-39 • OR: 1.5 (95% CI: 0.4-5.8), p =0.685 ≥40 • OR: 2.9 (95% CI: 0.9-9.1), p=0.202 0-17: Ref *Hospitalization, n/N (%):* Gender (male): • aOR: 0.8 (95% CI: 0.5-1.2), p=0.241 • OR: 0.7 (95% CI: 0.5-0.9), p=0.037 Age: 18-29 • aOR: 0.6 (95% CI: 0.4-1.0), p=0.06 • OR: 1.0 (95% CI: 0.8-1.4), p=0.883 30-39 • aOR: 0.8 (95% CI: 0.4-1.7), p =0.607 • OR: 1.5 (95% CI: 0.9-2.5), p=0.191 ≥40 • aOR: 1.3 (95% CI: 0.7-2.2), p=0.427

				• OR: 2.4 (95% CI: 1.6-3.6), p<0.001 0-17: Ref
Author: McClenaghan[2] **Year: 2020** **Data Extractor: DOS** **Reviewer: CS** **Study design: Cohort** **Study Objective: To describe the clinical characteristics and outcome of SARS-CoV-2 infection in 181 people with cystic fibrosis from 19 countries.** **IVA Score: 17 (high)**	**Population:** N=181 **Setting:** Hospitals and settings with CF teams **Location:** 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Ireland, Italy, Netherlands, New Zealand, Russia, Spain, South Africa, Sweden, Switzerland, UK, USA) **Study dates:** Up to June 13, 2020 **Inclusion criteria:** Data reported to the Cystic Fibrosis Registry Global Harmonization Group. People with CF reported by their CF team to have a diagnosis of acute SARS-CoV-2 infection. Diagnostic criteria were a positive nasal/throat PCR and/or CT scan, and/or firm clinical diagnosis in a hospital setting. **Exclusion criteria:** Incidental finding of raised serum SARS-CoV-2 antibodies as timing of acute infection would not be known.	**Health Condition Category:** Chronic Lung Disease, Risk Factors, Multiple Comorbid Conditions **Medical Condition, n/N (%):** Cystic fibrosis (CF): 181/181 (100%) • Post-transplant: 32/181 (17.7%) (28 lung-only transplants, 1 lung and kidney transplant, 2 liver-only transplants) • Non-transplant: 149/181 (82.3%) **Control/Comparison group, n/N (%):** None	**Medical Condition(s):** *CF:* ND **Severity Measure(s):** *Transplant status:* post-transplant or non-transplant *CF-related diabetes (CFRD):* ND *Best FEV_1:* prior to infection; categorized into <40, 40-70, and >70 **Clinical marker:** *F508del:* homozygous or heterozygous for F508del genotype **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* ND *Intubation:* NR *Ventilation:* non-invasive ventilation *Hospitalization:* ND *Non-elective readmissions*: NR **Comments:** Update to the Cosgriff 2020 paper.	**Severe COVID-19:** **Severity of Condition:** *Mortality, n/N (%):* Transplant status: • Post-transplant: 3/32 (9%) • Non-transplant: 4/149 (3%) • p=NR *ICU admission, n/N (%):* Transplant status: • Post-transplant: 7/28 (25%) • Non-transplant: 4/110 (4%) • p=NR CFRD among transplant patients: • CFRD: 6/17 (35%) • No CFRD: 1/7 (14%) CFRD among non-transplant patients: • CFRD: 1/22 (5%) • No CFRD: 3/82 (4%) Best FEV_1 among transplant patients: • <40: 0/0 • 40-70: 3/8 (38%) • >70: 2/16 (13%) Best FEV_1 among non-transplant patients: • <40: 0/14 (0%) • 40-70: 3/31 (10%) • >70: 1/52 (2%) *Ventilation, n/N (%):* Transplant status: • Post-transplant: 4/23 (17%) • Non-transplant: 3/101 (3%) • p=NR CFRD among non-transplant patients: • CFRD: 1/22 (5%) • No CFRD: 2/79 (3%) *Hospitalization, n/N (%):* Transplant status:

				• Post-transplant: 20/27 (74%) • Non-transplant: 66/141 (46%) • p=0.009 CFRD among transplant patients: • CFRD: 15/19 (79%) • No CFRD: 5/7 (71%) CFRD among non-transplant patients: • CFRD: 20/36 (56%) • No CFRD: 39/81 (48%) • p=0.460 Best FEV_1 among transplant patients: • <40: 1/1 (100%) • 40-70: 6/7 (86%) • >70: 8/12 (67%) Best FEV_1among non-transplant patients: • <40: 15/22 (68%) • 40-70: 27/38 (71%) • >70: 19/69 (28%) • p<0.001 **Duration of Condition:** NR **Clinical marker:** *ICU admission, n/N (%):* F508del among transplant patients: • Homozygous: 3/16 (19%) • Heterozygous: 3/9 (33%) • Other: 1/2 (50%) F508del among non-transplant patients: • Homozygous: 3/42 (7%) • Heterozygous: 1/41 (2%) • Other: 0/26 (0%) *Hospitalization, n/N (%):* F508del among transplant patients: • Homozygous: 12/16 (75%) • Heterozygous: 6/8 (75%) • Other: 2/2 (100%) F508del among non-transplant patients: • Homozygous: 23/52 (44%) • Heterozygous: 27/51 (53%) • Other: 16/37 (43%)

				Treatment/ Associated Therapy: NR **Comorbid Conditions:** NR **Risk Markers:** *ICU admission, n/N (%):* Sex among transplant patients: • Female: 0/11 (0%) • Male: 7/17 (41%) Sex among non-transplant patients: • Female: 2/58 (3%) • Male: 2/52 (4%) Age among transplant patients: • <18: 0/2 (0%) • 18-39: 4/14 (29%) • ≥40: 3/12 (25%) Age among non-transplant patients: • <18: 1/40 (3%) • 18-39: 1/52 (2%) • ≥40: 2/18 (11%) *Hospitalization, n/N (%):* Sex among transplant patients: • Female: 5/9 (56%) • Male: 15/18 (83%) Sex among non-transplant patients: • Female: 38/76 (50%) • Male: 28/65 (43%) • p=0.412 Age among transplant patients: • <18: 1/2 (50%) • 18-39: 11/14 (79%) • ≥40: 8/11 (73%) Age among non-transplant patients: • <18: 19/48 (40%) • 18-39: 34/70 (49%) • ≥40: 13/23 (57%) **Long-term Sequelae:** NR
Author: Moeller **Year: 2020** **Data Extractor: MW**	**Population:** N=185 cases with data on underlying conditions **Setting:** 180 centers	**Health Condition Category:** Chronic Lung Disease **Medical Condition, n/N (%):**	**Medical Condition(s):** *BPD:* ND *CF:* ND *Asthma:* ND	**Severe COVID-19:** *Mortality, n/N (%):* Bronchopulmonary dysplasia: • No deaths reported Cystic fibrosis:

Reviewer: DOS **Study Design: Cohort** **Study Objective: To determine the number of COVID-19 cases of children with pre-existing chronic respiratory conditions and whether they have exacerbations associated with SARS-CoV-2 virus.** **IVA Score: 16 (high)**	**Location:** Multiple Europe an countries **Study dates:** March 30 – May 3, 2020 **Inclusion criteria:** Survey responses from members of the ERS Pediatric Assembly on children who tested positive for SARS-CoV-2 at an institution were included. Additional data was collected on children with pre-existing chronic respiratory conditions. **Exclusion criteria:** NR	Bronchopulmonary dysplasia (BPD): 9/185 (4.8%) Cystic fibrosis (CF): 14/185 (7.5%) Asthma: 63/185 (34.1%) **Control/Comparison group, n/N (%):** No BPD: 176/185 (95.1%) No CF: 171/185 (92.4%) No asthma: 122/185 (65.9%)	**Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* Pediatric intensive care unit *Intubation:* NR *Ventilation:* Supplemental oxygen, noninvasive ventilation (NIV) or invasive ventilation *Hospitalization:* Pediatric ward and other unspecified wards *Non-elective readmissions*: NR **Comments:** None	• No deaths reported Asthma: • No deaths reported *ICU admission, n/N (%):* Bronchopulmonary dysplasia: • ICU: 2/9 (22.2%) • No ICU: 7/9 (77.7%) Cystic fibrosis: • ICU: 3/13 (23.1%) • No ICU: 5/8 (76.9%) Asthma: • ICU: 5/54 (9.3%) • No ICU: 49/54 (90.7%) *Ventilation, n/N (%):* Bronchopulmonary dysplasia: • Oxygen use was reported in three children and noninvasive ventilation in four infants Cystic fibrosis: • One child needed invasive ventilation and two needed supplemental oxygen Asthma: • 19 cases (39%) received supplemental oxygen and four children (8%) needed invasive ventilation *Hospitalization, n/N (%):* Bronchopulmonary dysplasia: • Hospitalized: 7/9 (77.7%) • Not hospitalized: 2/9 (22.2%) Cystic fibrosis: • Hospitalized: 7/13 (53.8%) • Not hospitalized: 6/13 (46.2%) Asthma: • Hospitalized: 38/54 (70.4%) • Not hospitalized: 16/54 (29.6%) **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR

				Risk Markers: NR **Long-term Sequelae:** NR
Author: Mondejar-Lopez **Year: 2020** **Data Extractor: MW** **Reviewer: CS** **Study Design: Cohort** **Study Objective: To determine the incidence of infection by the novel coronavirus and the impact of the first ten weeks of pandemic on the cohort of persons with cystic fibrosis (CF) as a possible population at risk of severe COVID-19, and to detail how Spanish CF Units have dealt with this health challenge for the purposes of adequate prevention of infection by the novel coronavirus, how clinical monitoring has been maintained, and how to explain the incidence observed in this group of patients.** **IVA Score: 19 (moderate)**	**Population:** N=8 **Setting:** CF units **Location:** Spain **Study dates:** March 8 – May 16, 2020 **Inclusion criteria:** Cases were identified as people with a confirmed diagnosis of CF who tested positive for SARS-CoV-2 PCR between the study dates and who were included in the European Cystic Fibrosis Society Patient Registry (ECFSPR). **Exclusion criteria:** CF patients and general population cases that were suspected but not confirmed by PCR or not tested due to low suspicion or mild symptoms and CF patients belonging to the Spanish CF Units that still do not participate in the ECFSP were excluded.	**Health Condition Category:** Chronic Lung Disease **Medical Condition, n/N (%):** CF: 8 **Control/Comparison group, n/N (%):** General population: NR	**Medical Condition(s):** *CF:* ND **Severity Measure(s):** NR **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* ND *Intubation:* NR *Ventilation:* ND *Hospitalization:* ND *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *Mortality rate:* • Cystic fibrosis: 0 deaths • General population: 5.85/10000 inhabitants *ICU admission:* • One patient had undergone lung transplantation two years before, had a baseline FEV1 of 88% and was on tacrolimus and mycophenolate mofetil therapy; this was the only one who was admitted to the ICU **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR **Risk Markers:** *Hospitalization:* • Both pediatric cases (2/8) were infected healthcare workers' children and the only ones not admitted to hospital, All the adults (6/8) required hospitalization *Ventilation:* • 4/6 hospitalized adults with CF needed supplementary oxygen, although none required mechanical ventilation **Long-term Sequelae:** NR
Author: Naehrlich[5]	**Population:** N= 130	**Health Condition Category:**	**Medical Condition(s):**	**Severe COVID-19:**

Year: 2021 **Data Extractor: MC** **Reviewer: DOS/MW** **Study design: Cohort** **Study Objective: To assess the incidence, clinical course, and outcome of SARS-CoV-2 infection in people with cystic fibrosis versus the general population** **IVA Score: 21 (moderate)**	**Setting:** NR **Location:** 38 European countries (Albania, Armenia, Austria, Belarus, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Republic of Moldova, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, & United Kingdom) **Study dates:** February 1,2020 - January 7, 2021 **Inclusion criteria:** People with cystic fibrosis diagnosed with PCR-confirmed SARS-CoV-2 infection between February 1 – June 30, 2020, and reported by one of the 38 European Cystic Fibrosis Society Patient Registry member countries **Exclusion criteria:** Patients seropositive for SARS-CoV-2 but without confirmatory PCR	Chronic lung disease **Medical Condition, n/N (%):** Cystic fibrosis: 130/130 (100%) **Control/Comparison group, n/N (%):** General population in corresponding countries: 2,582,924/832,750,755 (0.31%)	*Cystic fibrosis*: ND **Severity Measure(s):** *Lung-transplant status:* lung-transplanted (23/130 (17.7%)) and non-lung-transplanted people with cystic fibrosis (107/130 (82.3%)) **Clinical marker:** NR **Treatment/ Associated Therapy, n/N (%):** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* ND *Intubation:* invasive ventilation including ECMO *Ventilation:* non-invasive ventilation *Hospitalization:* ND *Non-elective readmissions*: NR **Comments:** Reporting was voluntary; therefore, cases may be under-reported with possible selection bias for more severe cases.	*Mortality, case fatality rate:* • Cystic fibrosis: 3.85% (95%CI: 1.26-8.75) • General population: 7.46% (95%CI: 7.43-7.49) • p=0.133 *ICU admission, n/N (%):* • Cystic fibrosis: 12/119 (10.08%) • General population: 15860/508098 (3.12%) • p<0.001 *Intubation, n/N (%):* • Cystic fibrosis: 5/80 (6.25%) *Ventilation, n/N (%):* • Cystic fibrosis: 5/80 (6.25%) *Hospitalization, n/N (%)* • Cystic fibrosis: 71/118 (60.17%) • General population: 145250/565695 (25.68%) • p<0.001 **Severity of Condition:** *Mortality, n/N (%):* Lung-transplant status: • Lung transplant: 3/23 (13%) • Non-lung transplant: 2/107 (1.9%) *ICU admission, n/N (%):* Lung-transplant status: • Lung transplant: 6/23 (26.1%) • Non-lung transplant: 6/107 (5.6%) *Hospitalization, n/N (%)* Lung-transplant status: • Lung transplant: 19/23 (82.6%) • Non-lung transplant: 56/107 (52.8%) **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 10. Internal Validity Assessments of Extracted Studies reporting the Association between Cystic Fibrosis and Severe COVID-19 Outcomes

Author Year	**Aveyard 2021**	**Bain 2021[3]**	**Beltramo 2021**	**Hadi 2021[4]**	**Jung 2021[1]**	**McClenaghan 2020[2]**	**Moeller 2020**	**Mondejar-Lopez 2020**	**Naehrlich 2021[5]**
Outcome(s)	Mortality, ICU, Hospitalization	ICU admission, ventilation, hospitalization	Mortality, ICU admission	Mortality, ICU admission, Ventilation, Hospitalization	Mortality, ICU admission, intubation, ventilation, hospitalization	Mortality, ICU admission, ventilation, hospitalization	Mortality, ICU admission, Hospitalization, Ventilation	Mortality	Mortality, ICU admission, intubation, ventilation, hospitalization
Signaling question	Data extracted from medical records	Data extracted from registry	Data extracted from hospital records	TriNETX research network (EMRs from > 40 healthcare organizations)	Data was collected from ECFSPR	data reported to CF registry by CF teams	Data collected from survey	Data extracted from national registry	Data collected from ECFSPR
Study Elements: **Design appropriate to research question**	1	1	1	1	1	1	1	1	1
Well described population	1	1	1	1	1	1	1	1	1
Well described setting	1	1	1	1	1	1	1	1	1
Well described intervention/ exposure	1	1	1	1	1	1	1	1	1
Well described control/ comparator	1	0	1	1	0	0	1	0	0
Well described outcome	1	1	1	1	1	1	1	1	1
Clear timeline of exposures/ interventions and outcomes	1	1	0	1	1	1	1	1	1
Selection Bias: Sampling **Randomization**	0	0	0	0	0	0	0	0	0

appropriately performed									
Allocation adequately concealed	0	0	0	0	0	0	0	0	0
Population sampling appropriate to study design	1	1	1	1	1	0	1	1	1
Selection Bias: Attrition **Attrition not significantly different between groups**	1	1	1	1	0	1	0	1	1
Attrition <10-15% of population	1	1	1	1	0	1	1	1	1
Attrition appropriately analyzed	1	1	1	1	0	1	1	1	1
Information Bias: Measurement and Misclassification **Measure of intervention/ exposure is valid**	1	1	1	0	1	1	1	1	1
Measure of outcome is valid	1	1	1	1	1	1	0	1	1
Fidelity to intervention is measured	0	0	0	0	0	0	0	0	0
Fidelity to intervention is valid	0	0	0	0	0	0	0	0	0
Prospective study	1	1	1	1	1	1	1	1	1
Adequately powered to detect result	0	0	0	0	0	0	0	0	0
Information Bias: Performance & Detection	0	0	0	0	0	0	0	0	0

Outcome assessor blinded									
Study participant blinded	0	0	0	0	0	0	0	0	0
Investigator/ data analyst blinded	0	0	0	0	0	0	0	0	0
Data collection methods described in sufficient detail	1	1	1	1	1	0	1	1	1
Data collection methods appropriate	1	1	1	1	1	1	0	1	1
Sufficient follow up to detect outcome	1	1	1	1	1	1	1	1	1
Information Bias: Analytic **Appropriate statistical analyses for collected data**	1	0	1	1	1	0	0	0	1
Appropriate statistical analyses are conducted correctly	1	0	1	1	1	0	0	0	1
Confidence interval is narrow	0	0	1	1	0	0	0	0	0
Confounding**: Potential confounders identified**	1	0	1	1	1	1	0	0	1
Adjustment for confounders in study design phase	0	0	0	0	0	0	0	0	1
Adjustment for confounders in data analysis phase	1	0	1	1	1	0	0	0	0
Reporting Bias: **All pre-specified**	1	1	1	1	1	1	1	1	1

outcomes are adequately reported									
Other Bias: **No other sources of bias**	1	1	1	1	0	1	1	1	0
COI: **Funding sources disclosed and no obvious conflict of interest**	1	1	1	1	1	1	1	1	1
SCORE: Threat to internal validity	24	19	24	24	19	18	17	19	22
Low, Moderate, High	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	High	Moderate	Moderate

C. References

1. Jung A, Orenti A, Dunlevy F, et al. Factors for severe outcomes following SARS-CoV-2 infection in people with cystic fibrosis in Europe. *ERJ Open Res*. Oct 2021;7(4)doi:10.1183/23120541.00411-2021
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3. Bain R, Cosgriff R, Zampoli M, et al. Clinical characteristics of SARS-CoV-2 infection in children with cystic fibrosis: An international observational study. *J Cyst Fibros*. Jan 2021;20(1):25-30. doi:10.1016/j.jcf.2020.11.021
4. Hadi YB, Lakhani DA, Naqvi SF, Fatima NU, Sarwari AR. Outcomes of SARS-CoV-2 infection in patients with cystic fibrosis: A multicenter retrospective research network study. *Respir Med*. Nov 2021;188:106606. doi:10.1016/j.rmed.2021.106606
5. Naehrlich L, Orenti A, Dunlevy F, et al. Incidence of SARS-CoV-2 in people with cystic fibrosis in Europe between February and June 2020. *J Cyst Fibros*. Jul 2021;20(4):566-577. doi:10.1016/j.jcf.2021.03.017

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

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
MOA	measure(S) of association
ND	not defined
NR	not reported
OR	odds ratio
PECO	population, exposure, comparator, and outcomes
RT-PCR	real time polymerase chain reaction