

## **Brief Summary of Findings on the Association Between Alpha-1 Antitrypsin Deficiency and Severe COVID-19 Outcomes**

Prepared and reviewed by:

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

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

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

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

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

**Aisha L. Hill, PhD, MS**, Public Health Analyst II, St. George Tanaq Corporation

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

**Christine N. So, MPH**, Program Analyst III; Eagle Global Scientific

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

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

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

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

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

Contact: [CDC Info contact us form](#)

## **Brief Summary of Findings on the Association Between Alpha-1 Antitrypsin Deficiency and Severe COVID-19 Outcomes**

Six studies were included for analysis. Three cohort studies, two ecological studies, and one case report were retrieved that reported data on underlying Alpha-1 Antitrypsin Deficiency (A1AT) and severe COVID-19 outcomes.

- The evidence is inconsistent and inconclusive on the association between A1AT and mortality<sup>1-5</sup>, ICU admission<sup>1, 5</sup> intubation<sup>5</sup>, ventilation<sup>5, 6</sup>, and hospitalization<sup>1, 5, 6</sup>. Evidence was also insufficient to determine if the relationship between A1AT and mortality was influenced by severity or confounding with other underlying conditions.

## Contents

Table of Tables.....	3
List of Figures.....	4
A. Methods .....	5
A.1. Literature Search.....	5
A.2. Study Selection.....	5
A.4. Data Extraction and Synthesis.....	8
A.5. Aggregation of the Evidence .....	8
A.6. Reviewing and Finalizing the Systematic Review .....	8
B. Systematic Literature Review Results .....	9
B.1. Search Strategies and Results .....	9
B.2. Study Inclusion and Exclusion Criteria.....	11
B.3. Evidence Review: Alpha-1 Antitrypsin (A1AT) Deficiency and Severe COVID-19 .....	13
B.3.a. Strength & Direction of Evidence .....	13
B.3.b. Extracted Evidence .....	18
B.3.c. Internal Validity Assessments of Extracted Studies.....	24
C. References.....	26

## Table of Tables

<b>Table 1</b> Alpha-1 Antitrypsin Deficiency Search Conducted July 19, 2021.....	9
<b>Table 2</b> The Association Between A1AT Deficiency and Severe COVID-19 Outcomes .....	13
<b>Table 3</b> Increasing Severity of Underlying A1AT Deficiency and Severe COVID-19 Outcomes.....	16
<b>Table 4</b> Risk Markers of Underlying A1AT Deficiency Examined for Association With Severe COVID-19 Outcomes.....	17
<b>Table 5</b> Comorbid Conditions and Underlying A1AT Deficiency Examined for Association With Mortality Due to COVID-19 .....	17
<b>Table 6</b> Extracted Studies Reporting the Association Between A1AT Deficiency and Severe COVID-19 Outcomes .....	18
<b>Table 7</b> Internal Validity Assessments of Extracted Studies Reporting the Association Between A1AT Deficiency and Severe COVID-19 Outcomes .....	24

## List of Figures

Figure 1. Results of the Study Selection Process .....	6
--	---

## A. Methods

The aim of this review was to identify and synthesize the best available evidence on the association between alpha-1 antitrypsin (A1AT) deficiency and severe COVID-19 outcomes to update the Centers for Disease Control and Prevention (CDC) website on underlying conditions for a consumer and a provider-specific website with more rigorous information.

### A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, and outcomes (PECO) question. Clinical experts and library scientists were consulted to develop a robust list of search terms. These terms were then incorporated into search strategies, and these searches were performed in OVID using the COVID-19 filter for all articles from the beginning of each database until July 19, 2021. The detailed search strategies for identifying primary literature and the search results are provided in *Part B*. References were included if retrieved by the literature search and reported exposures and outcomes relevant to this review.

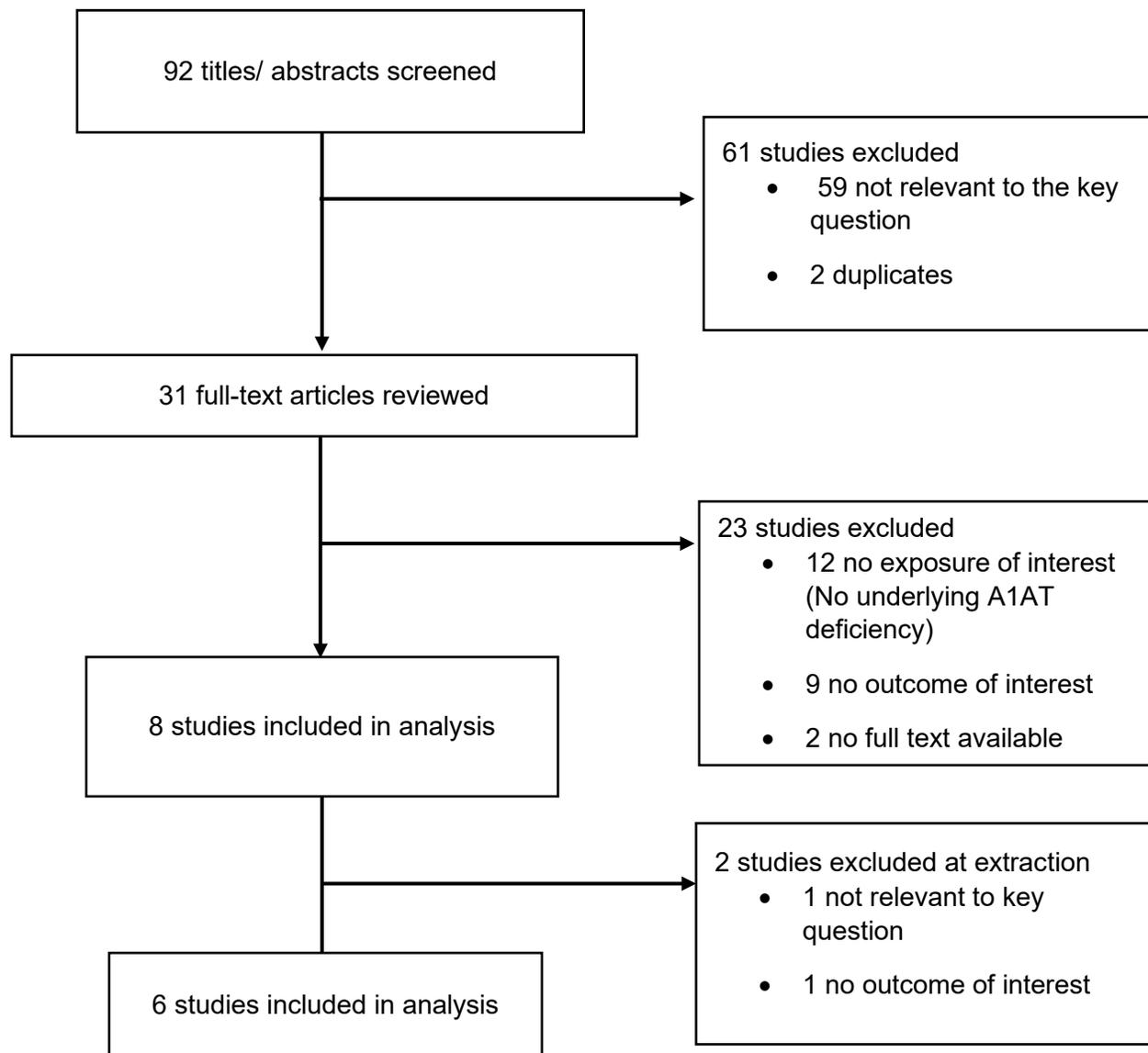
### A.2. Study Selection

Titles and abstracts from references were screened by dual review (A.H., M.M., D.O.S., or E.C.S.). Full-text articles were retrieved if they were:

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

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

**Figure 1. Results of the Study Selection Process**





#### **A.4. Data Extraction and Synthesis**

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

#### **A.5. Aggregation of the Evidence**

The internal validity associated with each study was assessed using scales developed by the Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. The *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 the *Part B*.

#### **A.6. Reviewing and Finalizing the Systematic Review**

Draft findings, aggregation tables, and evidence tables, were 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** Alpha-1 Antitrypsin Deficiency Search Conducted July 19, 2021.

Database	Strategy	Records 07/19/2021
<b>Medline (OVID) 1946-</b>	Alpha 1 antitrypsin OR a1 antitrypsin OR a-1 antitrypsin OR A1AT deficiency OR A1AD AND Limit COVID-19 (validated filter) 2020- ;	32
<b>Embase (OVID) 1988-</b>	Alpha 1 antitrypsin OR a1 antitrypsin OR a-1 antitrypsin OR A1AT deficiency OR A1AD AND Limit COVID-19 (validated filter)  2020- ; NOT pubmed/medline	62  -29 duplicates  =33 unique items
<b>Global Health (OVID)</b>	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) AND Alpha 1 antitrypsin OR a1 antitrypsin OR a-1 antitrypsin OR A1AT deficiency OR A1AD 2020-	11  -9 duplicates  =2 unique items
<b>CAB Abstracts (OVID)</b>	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) AND Alpha 1 antitrypsin OR a1 antitrypsin OR a-1 antitrypsin OR A1AT deficiency OR A1AD 2020-	3  -3 duplicates  =0 unique items
<b>PsycInfo (OVID) 1987-</b>	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*)	0

Database	Strategy	Records 07/19/2021
	AND Alpha 1 antitrypsin OR a1 antitrypsin OR a-1 antitrypsin OR A1AT deficiency OR A1AD 2020-	
<b>CINAHL (EbscoHost)</b>	("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR covid OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR "wuhan virus*") AND "Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT deficiency OR A1AD 2020- ;	2  -2 duplicates  =0 unique items
<b>Academic Search Complete</b>	("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR covid OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR "wuhan virus*") AND "Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT deficiency OR A1AD 2020- ;	7  -2 duplicates  =5 unique items
<b>Scopus</b>	TITLE-ABS("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR covid OR nCoV OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus" ) AND TITLE-ABS("Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT deficiency OR A1AD)  2020- ; English;	27  -25 duplicates  =2 unique items
<b>WHO Global COVID Literature Database</b>	"Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT deficiency OR A1AD	24  -24 duplicates  =0 unique items

Database	Strategy	Records 07/19/2021
Coronavirus Research Database	TI,AB("Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT deficiency OR A1AD)	13  -9 duplicates  =4 unique items
Cochrane Library	"Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT deficiency OR A1AD AND "novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus"	8  -2 duplicates  =6 unique items
Clinicaltrials.gov	"Alpha 1 antitrypsin" OR "a1 antitrypsin" OR "a-1 antitrypsin" OR A1AT DEFICIENCY OR A1AD   "novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus"	8

## B.2. Study Inclusion and Exclusion Criteria

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

- were relevant to the key question “What is the association between alpha-1 antitrypsin deficiency and severe COVID-19?”;
  - exposures: Alpha-1 Antitrypsin (A1AT) Deficiency.
  - outcomes: mortality, ICU admission, intubation, ventilation, and hospitalization
- were primary research;
- were written in English (can be seen as [language] in title); and
- examined humans only.

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

- were not available as full-text;
- were a conference abstract, poster, or reply letter;

- reported autopsy results; and
- reported only composite outcome measures for “severe covid-19”.

### B.3. Evidence Review: Alpha-1 Antitrypsin (A1AT) Deficiency and Severe COVID-19

#### B.3.a. Strength & Direction of Evidence

**Table 2** The Association Between A1AT Deficiency and Severe COVID-19 Outcomes

Outcome	Results
Mortality	<p>Overall, data from five studies<sup>1-5</sup> (N = 14,402) is inconsistent and inconclusive on an association between underlying <math>\alpha</math>-1 antitrypsin deficiency (A1AT deficiency) and mortality. Two studies<sup>2, 3</sup> were found to have a high threat to internal validity, while one study<sup>4</sup> was found to have a moderate threat to internal validity. Internal validity assessments are not completed for studies<sup>1, 5</sup> with less than 10 people with A1AT deficiency.</p> <ul style="list-style-type: none"> <li>• Strength of Association: One small study reported a measure of association suggesting no difference.<sup>1</sup></li> <li>• Precision of Association: No studies reported confidence intervals.</li> <li>• Consistency of Association: Overall, the evidence is inconsistent.</li> <li>• Applicability of Association: The population and setting were directly applicable to the question. Two studies<sup>1, 2</sup> were conducted in European countries, two studies<sup>3, 4</sup> were conducted internationally, and one study<sup>5</sup> was conducted in the U.S. Studies were conducted among adults of all age groups including population-level, community, and hospital settings.</li> </ul> <p>Summary of Evidence:</p> <ul style="list-style-type: none"> <li>• Two ecological studies<sup>3, 4</sup> (N = NR) reported correlation coefficients suggesting a positive correlation between mortality and A1AT deficiency in people with COVID-19. <ul style="list-style-type: none"> <li>▪ One cross-sectional ecological study<sup>3</sup> (N = NR) reported a moderate positive correlation suggests an association of national rates of A1AT deficiency with the national rates of COVID-19 fatalities [R = 0.54, p &lt; 0.01]. This correlation remained significant even after adjusting for the human development index.</li> <li>▪ One ecological study<sup>4</sup> (N = NR) reported data suggesting a strong correlation between global COVID-19 mortality and A1AT deficiency [R = 0.86, p = NR]. This correlation remained strong in a sub-analysis of data from European, and North and South American countries [R = 0.89, p = NR] but did not persist in a sub-analysis of data from Asian and African countries [R = 0.025, p = NR].</li> </ul> </li> <li>• Three studies<sup>1, 2, 5</sup> (N = 14,402) reported proportions suggesting no association between mortality and A1AT deficiency among people with COVID-19. <ul style="list-style-type: none"> <li>▪ One telephone survey<sup>1</sup> (N = 8) of Italians with severe A1AT deficiency reported eight cases of self-reported COVID-19+ status, with a mortality rate [12.5% (1/8)] similar to the mortality rate in the national population [13.9% (RR: 0.90)]. The survey only reached 35% of the Italian cohort with severe A1AT deficiency.</li> </ul> </li> </ul>

Outcome	Results
	<ul style="list-style-type: none"> <li>▪ One cohort study<sup>2</sup> (N = 14,393) of people tested for genotype variants, suggested similar proportions of mortality among people with A1AT deficiency and COVID-19 compared to those with only COVID-19 [3.17% (53/1,670) vs. 2.77% (353/12,723)].</li> <li>▪ One case report<sup>5</sup> (N = 1) reported an immunosuppressed 67-year-old female with homozygous Z-allele mutation A1AT deficiency and COVID-19 who did not die. The patient had a history of several comorbidities, including liver transplant, chronic kidney disease stage IIIa, cirrhosis, COPD, hypertension, deep venous thrombosis, and uncontrolled insulin-dependent type 2 diabetes mellitus. Internal validity is not assessed for case reports.</li> </ul>
ICU Admission	<p>Overall, limited data from two studies<sup>1, 5</sup> (N = 9) is inconclusive on the association between underlying A1AT deficiency and ICU admission. Internal validity assessments are not completed for studies<sup>1, 5</sup> with less than 10 people with A1AT deficiency.</p> <ul style="list-style-type: none"> <li>• Strength of Association: No studies reported measures of association.</li> <li>• Precision of Association: No studies reported confidence intervals.</li> <li>• Consistency of Association: Overall, the number of events, and sample sizes were too small to determine consistency.</li> <li>• Applicability of Association: The population and setting were directly applicable to the question. One study<sup>1</sup> was conducted in a European country, and one<sup>5</sup> was conducted in the U.S. Studies were conducted among adults in community and hospital settings.</li> </ul> <p>Summary of Evidence:</p> <ul style="list-style-type: none"> <li>• Two studies<sup>1, 5</sup> reported proportions or cases on ICU admission and A1AT deficiency in COVID-19 patients. <ul style="list-style-type: none"> <li>▪ One cohort study<sup>1</sup> (N = 8) of Italians with severe A1AT deficiency and COVID-19 reported an ICU admission rate of 0% (0/8) among patients with COVID-19 and underlying A1AT deficiency.</li> <li>▪ One case report<sup>5</sup> (N = 1) of an immunosuppressed 67-year-old female with homozygous Z-allele mutation A1AT deficiency in Pennsylvania, US reported that the patient was upgraded to the Medical intensive care unit (MICU) after presenting with COVID-19 mediated hypoxic respiratory failure. The patient had a history of several comorbidities, including liver transplant, chronic kidney disease stage IIIa, cirrhosis, COPD, hypertension, deep venous thrombosis, and uncontrolled insulin-dependent type 2 diabetes mellitus. Internal validity is not assessed for case reports.</li> </ul> </li> </ul>
Intubation	<p>Overall, limited evidence from one study is insufficient to determine an association between A1AT deficiency and intubation. Aggregation indices are not evaluated for outcomes reported by only one study.</p>

Outcome	Results
	<ul style="list-style-type: none"> <li>▪ One case report<sup>5</sup> (N = 1) reported intubation in an immunosuppressed 67-year-old female with homozygous Z-allele mutation A1AT deficiency after presenting with COVID-19 mediated hypoxic respiratory failure. Internal validity is not assessed for case reports.</li> </ul>
Ventilation	<p>Overall, the evidence from two studies<sup>5,6</sup> (N = 10) is inconsistent and inconclusive on an association between underlying A1AT deficiency and ventilation. Internal validity assessments are not completed for studies<sup>5,6</sup> with less than 10 people with A1AT deficiency.</p> <ul style="list-style-type: none"> <li>• Strength of Association: No studies reported measures of association.</li> <li>• Precision of Association: No studies reported confidence intervals.</li> <li>• Consistency of Association: Overall, the number of events, and sample sizes were too small to determine consistency.</li> <li>• Applicability of Association: The population and setting were directly applicable to the question. One study<sup>5</sup> was conducted in the U.S., and one study was conducted in a European country. Studies were conducted among adults in hospital settings.</li> </ul> <p>Summary of Evidence:</p> <ul style="list-style-type: none"> <li>• Two studies<sup>5,6</sup> (N = 10) reported data on ventilation and A1AT deficiency in COVID-19 patients. <ul style="list-style-type: none"> <li>▪ One cohort<sup>6</sup> (N = 9) reported the proportion of COVID-19 patients with A1AT deficiency that required ventilation [0% (0/77)]. This study had a small sample size with a low number of events and no comparison group, decreasing confidence in the finding.</li> <li>▪ One case report<sup>5</sup> (N = 1) of a 67-year-old female with A1AT deficiency in Pennsylvania, US reported that the patient was mechanically ventilated. Internal validity is not assessed for case reports.</li> </ul> </li> </ul>
Hospitalization	<p>Overall, the evidence from three studies<sup>1,5,6</sup> (N = 18) is consistent, but inconclusive on an association between underlying A1AT deficiency and hospitalization. Internal validity assessments are not completed for studies<sup>1,5,6</sup> with less than 10 people with A1AT deficiency.</p> <ul style="list-style-type: none"> <li>• Strength of Association: No studies reported measures of association.</li> <li>• Precision of Association: No studies reported confidence intervals.</li> <li>• Consistency of Association: Descriptive statistics are consistent across studies.</li> </ul>

Outcome	Results
	<ul style="list-style-type: none"> <li>• Applicability of Association: The population and setting were directly applicable to the question. Two studies<sup>1, 6</sup> were conducted in European countries, and one study<sup>5</sup> was conducted in the U.S. Studies were conducted among adults in hospital settings.</li> </ul> <p>Summary of Evidence:</p> <ul style="list-style-type: none"> <li>▪ Three studies<sup>1, 5, 6</sup> reported data on hospitalization and A1AT deficiency in COVID-19 patients. <ul style="list-style-type: none"> <li>▪ One cohort study<sup>1</sup> (N = 8) using telephone survey data reported the proportions of participants with underlying A1AT deficiency that were hospitalized among people with COVID-19 [37.5% (3/8)]. The study did not have a comparison group for this outcome and had a small sample size with a low number of events, decreasing confidence in this finding.</li> <li>▪ One cohort study<sup>6</sup> (N = 9) reported the proportion of participants with underlying A1AT deficiency that were hospitalized [4% (3/77)]. This study had a small sample size with a low number of events and no comparison group, decreasing confidence in the finding.</li> <li>▪ One case report<sup>5</sup> (N = 1) of a 67-year-old female with A1AT deficiency in Pennsylvania, US reported that the patient was admitted to the hospital. Internal validity is not assessed for case reports.</li> </ul> </li> </ul>

**Table 3** Increasing Severity of Underlying A1AT Deficiency and Severe COVID-19 Outcomes

Outcome	Results
Mortality	<p>Overall, the evidence is inconsistent and inconclusive on an association between the severity markers of A1AT deficiency and mortality. One study was found to have moderate<sup>4</sup> and the other study<sup>2</sup> was found to have high threat to internal validity.</p> <ul style="list-style-type: none"> <li>• Strength of Association: The correlation coefficient ranged from 0.025 - 0.950.</li> <li>• Precision of Association: Confidence intervals were not reported.</li> <li>• Consistency of Association: Evidence is inconsistent</li> <li>• Applicability of Association: The population and setting were directly applicable to the question. One study<sup>2</sup> was conducted in Europe and one<sup>4</sup> was conducted internationally.</li> </ul> <p>Summary of Evidence:</p> <ul style="list-style-type: none"> <li>• Two studies<sup>2, 4</sup> reported data on mortality and A1AT deficiency genotypes in COVID-19 patients.</li> </ul>

	<ul style="list-style-type: none"> <li>▪ One ecological study<sup>4</sup> (N = 68 countries) reported a stronger correlation between COVID-19 and mortality in populations with the underlying PiZ genotype than in populations with the PiS genotype.</li> <li>▪ One cohort study<sup>2</sup> (N = 14,393) of Biobank and national death registries data in the United Kingdom reported on people with different genotypes representing severity of A1AT deficiency. While proportions of mortality were consistent across the genotypes, no conclusions can be drawn from this study because of a small number of events and lack of statistical significance.</li> </ul>
--	---

**Table 4** Risk Markers of Underlying A1AT Deficiency Examined for Association With Severe COVID-19 Outcomes

Risk Marker	Results
Smoking (median pack/year)	<p>Overall, limited evidence from one study is insufficient to determine an association between hospitalization in people with COVID-19 and underlying A1AT deficiency who smoked. Aggregation indices are not evaluated for outcomes reported by only one study.</p> <ul style="list-style-type: none"> <li>• One cohort study<sup>6</sup> reported hospitalization in smokers with A1AT deficiency among people with COVID-19. <ul style="list-style-type: none"> <li>▪ One cohort study<sup>6</sup> (N = 9) of a national COVID-19 status database and pulmonology records reported [33.3% (3/9)] people with A1AT deficiency and COVID-19 were hospitalized. These people were more likely to be heavier smokers than those who were not hospitalized [66.6% (6/9)].</li> </ul> </li> </ul>
Baseline diffusion capacity (mean %)	<p>Overall, limited evidence is inconclusive to determine an association between hospitalization and low baseline diffusion capacity [DLCO] in people with COVID-19 with underlying A1AT deficiency. Aggregation indices are not evaluated for outcomes reported by only one study.</p> <ul style="list-style-type: none"> <li>• One cohort study<sup>6</sup> reported hospitalization in people with a lower baseline DLCO with A1AT deficiency among people with COVID-19. <ul style="list-style-type: none"> <li>▪ One cohort study<sup>6</sup> (N = 9) of national COVID-19 status database and pulmonology records reported that with underlying A1AT deficiency and COVID-19 and acute respiratory failure (ARF) who were hospitalized [33.3% (3/9)] were more likely to have a lower baseline DLCO than those who were not hospitalized [66.6% (6/9)].</li> </ul> </li> </ul>

**Table 5** Comorbid Conditions and Underlying A1AT Deficiency Examined for Association With Mortality Due to COVID-19

Comorbid condition	Results

Severe lung impairment	<p>Overall, limited evidence is inconclusive to determine an association between severe lung impairment and mortality in people with COVID-19 and underlying A1AT deficiency. Aggregation indices are not evaluated for outcomes reported by only one study.</p> <ul style="list-style-type: none"> <li>• One cohort study<sup>1</sup> reported hospitalization in an individual with A1AT deficiency and severe lung impairment prior to COVID-19 illness. <ul style="list-style-type: none"> <li>▪ One cohort study<sup>1</sup> (N = 8) of patients with severe A1AT deficiency reported on eight patients with COVID-19 and the one patient that died was already hospitalized because of severe lung impairment prior to COVID-19 illness . This study had a small sample size with a low number of events, decreasing confidence in this finding.</li> </ul> </li> </ul>
------------------------	---

### B.3.b. Extracted Evidence

**Table 6** Extracted Studies Reporting the Association Between A1AT Deficiency and Severe COVID-19 Outcomes

Study	Population and Setting	Exposure	Definitions	Results
<p><b>Author:</b> De Souza<sup>5</sup></p> <p><b>Year:</b> 2020</p> <p><b>Data Extractor:</b> AH</p> <p><b>Reviewer:</b> DOS</p> <p><b>Study design:</b> Case report</p> <p><b>Study Objective:</b> NR</p> <p><b>IVA Score:</b> Not completed</p>	<p><b>Population:</b> N = 1</p> <p><b>Setting:</b> Hospital</p> <p><b>Location:</b> PA, US</p> <p><b>Study dates:</b> April 4 – May 11, 2020</p> <p><b>Inclusion criteria:</b> NR</p> <p><b>Exclusion criteria:</b> NR</p>	<p><b>Medical Condition, n/N (%):</b> Alpha-1 antitrypsin (A1AT) deficiency: 1/1 (100%)</p>	<p><b>Medical Condition(s):</b> <i>A1AT deficiency:</i> hereditary co-dominant disorder resulting from the replacement of a single amino acid in the serine protease inhibitor clade A-member-1 (SERPINA1) gene on the long arm of chromosome 14; characterized by either the complete absence of the ATT-1 enzyme (homozygote genotype PiZZ) or a misfolded A1AT enzyme (heterozygote genotype PiMZ), which can promote early-onset emphysema due to “loss of function mutation” and/or the retainment of misfolded protein within hepatocytes leading to cirrhosis</p> <p><b>Severity Measure(s):</b> <i>Homozygous Z-allele mutation:</i> ND</p> <p><b>Clinical marker:</b> NR</p>	<p><b>Severe COVID-19:</b> <i>Mortality:</i> No <i>ICU admission:</i> Yes, MICU <i>Intubation (or Invasive Ventilation):</i> Yes, Intubation <i>Ventilation (mechanical, or non-invasive ventilation):</i> Yes, Mechanical <i>Hospitalization:</i> Yes</p> <p><b>General Progression</b></p> <ul style="list-style-type: none"> <li>• <i>Case 1:</i> An immunosuppressed 67-year-old female with homozygous Z-allele mutation A1AT deficiency admitted to hospital due to dyspnea and cough and tested positive for COVID-19 via real-time RT-PCR. Home medications included tacrolimus, mycophenolate, and prednisone. Patient was upgraded to COVID-19 designated MICU, requiring sedation, intubation, and medical ventilation. Given a low dose of norepinephrine by infusion and started treatment with ceftriaxone, doxycycline, and hydroxychloroquine. Hydroxychloroquine was stopped prematurely due to QTc prolongation. Patient’s vasopressor requirement continued to increase, and she was placed on thiamine, ascorbic acid, and stress dose steroids. The patient was placed on continuous renal replacement therapy on hospital day 6. During the second week of hospitalization, patient’s clinical status declined. Chest X-ray showed increased opacities in the right lung base and ultrasound showed a hyperdynamic ejection fraction. She</li> </ul>

			<p><b>Outcome Definitions:</b>  <i>Mortality:</i> ND  <i>ICU admission:</i> MICU  <i>Intubation:</i> ND  <i>Ventilation:</i> mechanical ventilation  <i>Hospitalization:</i> ND  <i>Non-elective readmissions:</i> NR</p> <p><b>Comments:</b> None</p>	<p>received empiric treatment for ventilation-acquired pneumonia and a 7-day course of piperacillin-tazobactam. On hospital day 9, she was weaned off norepinephrine, cisatracurium, and hydrocortisone. Patient remained on continuous veno-veno-hemodiafiltration for 10 days and was extubated and transitioned to intermittent hemodialysis on hospital day 16. The patient had a repeat positive COVID-19 test, but her mental status showed improvement. She was downgraded from the MICU to the intermediate medical care unit where she completed a 10-day course of oral vancomycin after testing positive for <i>Clostridium difficile</i>. She continued to improve and following 2 negative COVID-19 tests and the removal of her dialysis catheter, she was discharged to a local rehabilitation center and then discharged home.</p> <p><b>Severity of Condition:</b></p> <ul style="list-style-type: none"> <li>• <i>Case 1:</i> homozygous Z-allele mutation A1AT deficiency</li> </ul> <p><b>Duration of Condition:</b> NR</p> <p><b>Comorbid Conditions/ History of Disease:</b></p> <ul style="list-style-type: none"> <li>• <i>Case 1:</i> Liver transplant patient with chronic kidney disease stage IIIa, cirrhosis, COPD, hypertension, deep venous thrombosis, uncontrolled insulin-dependent type 2 diabetes mellitus</li> </ul> <p><b>Risk Markers:</b> NR</p> <p><b>Long-term Sequelae:</b>  Non-elective readmissions: Not applicable for this study type</p>
<p><b>Author:</b> Faria<sup>6</sup>  <b>Year:</b> 2021  <b>Data Extractor:</b> MM  <b>Reviewer:</b> DOS  <b>Study Design:</b> Retrospective cohort</p>	<p><b>Population:</b> N = 77  COVID-19+ N = 9</p> <p><b>Setting:</b> Tertiary hospital</p> <p><b>Data Source:</b> national COVID-19 status database and pulmonology records</p>	<p><b>Medical Condition, n/N (%):</b>  A1AT deficiency: 77/77 (100%)</p> <p><b>Control/Comparison Group, n/N (%):</b> NA</p>	<p><b>Medical Condition(s):</b>  A1AT deficiency: ND</p> <p><b>Severity Measure(s):</b> NR</p> <p><b>Clinical Marker:</b> NR</p> <p><b>Outcome Definitions:</b>  <i>Mortality:</i> NR  <i>ICU admission:</i> NR  <i>Intubation:</i> NR</p>	<p><b>Severe COVID-19:</b>  <i>Hospitalization, n/N (%):</i></p> <ul style="list-style-type: none"> <li>• Hospitalization: 3/77 (4%)</li> <li>• No hospitalization: 74/77 (96%)</li> </ul> <p>All patients hospitalized had acute respiratory failure.</p> <p><i>Ventilation, n/N (%):</i></p> <ul style="list-style-type: none"> <li>• Ventilation: 0/77 (0%)</li> <li>• No ventilation: 77/77 (100%)</li> </ul>

<p><b>Study Objective:</b> To address the risk of COVID-19 infection in a cohort of Alpha-1 Antitrypsin (A1AT) Deficiency patients through a comparison of A1AT patients with and without COVID-19.</p> <p><b>IVA Score:</b> 16 (High)</p>	<p><b>Location:</b> Portugal</p> <p><b>Study Dates:</b> NR - January 2021</p> <p><b>Inclusion Criteria:</b> All A1AT deficient patients followed at pulmonary consultation at study hospital.</p> <p><b>Exclusion Criteria:</b> NR</p>		<p><b>Ventilation:</b> Non-invasive ventilation or high flow nasal cannula</p> <p><b>Hospitalization:</b> hospitalized due to acute respiratory failure</p> <p><b>Non-elective readmissions:</b> NR</p> <p><b>Comments:</b> None</p>	<p><b>Severity of Condition:</b> NR</p> <p><b>Duration of Condition:</b> NR</p> <p><b>Comorbid Conditions:</b> NR</p> <p><b>Risk Markers:</b></p> <p><i>Smoking, pack/year, Mean ± std dev:</i></p> <ul style="list-style-type: none"> <li>Hospitalized: 30 ±25.2 pack/year</li> <li>Not hospitalized: 5.2 ±2.9 pack/year</li> <li>p=0.09</li> </ul> <p><i>Baseline Diffusion Capacity, Mean % ± std dev:</i></p> <ul style="list-style-type: none"> <li>Hospitalized: 53.0% ±18.8%</li> <li>Not hospitalized: 87.8% ±4.6%</li> <li>p=0.042</li> </ul> <p><b>Long-term Sequelae:</b></p> <p>Non-elective readmissions: NR</p>
<p><b>Author:</b> Ferrarotti<sup>1</sup></p> <p><b>Year:</b> 2021</p> <p><b>Data Extractor:</b> MM</p> <p><b>Reviewer:</b> DOS</p> <p><b>Study Design:</b> Cohort</p> <p><b>Study Objective:</b> To investigate whether people with severe AAT deficiency (A1AT deficiency) have an increased risk of severe COVID-19.</p>	<p><b>Population:</b> N = 209 COVID-19+ N = 8</p> <p><b>Setting:</b> Community</p> <p><b>Data Source:</b> Telephone survey and Istituto Superiore di Sanita</p> <p><b>Location:</b> Italy</p> <p><b>Study Dates:</b> May 2020</p> <p><b>Inclusion Criteria:</b> Subjects aged over 18 years old with severely reduced serum AAT levels due to two inherited pathological alleles in the SERPINA1 gene were surveyed via</p>	<p><b>Medical Condition, n/N (%):</b> A1AT deficiency: 8/8 (100%)</p> <p><b>Control/Comparison Group, n/N (%):</b> General population in Italy: NR</p>	<p><b>Medical Condition(s):</b> A1AT deficiency: the most abundant serum proteinase, whose deficiency caused by pathological mutation(s) in the SERPINA1 gene results in an imbalance in proteinase activity which may lead to proteolytic tissue damage and premature emphysema and COPD</p> <p><b>Severity Measure(s):</b> NR</p> <p><b>Clinical Marker:</b> NR</p> <p><b>Outcome Definitions:</b> <i>Mortality:</i> ND <i>ICU admission:</i> intensive care <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> ND</p>	<p><b>Severe COVID-19:</b> <i>RR: Relative Risk</i></p> <p><i>Mortality, n/N (%):</i></p> <ul style="list-style-type: none"> <li>RR: 0.9</li> <li>A1AT deficiency: 1/8 (12.5%)</li> <li>General Italian population: N = NR/N = NR (13.9%)</li> </ul> <p><i>ICU admission, n/N (%):</i></p> <ul style="list-style-type: none"> <li>Admitted to ICU: 0/8 (0%)</li> <li>Not admitted to ICU: 8/8 (100%)</li> </ul> <p><i>Hospitalization, n/N (%):</i></p> <ul style="list-style-type: none"> <li>Hospitalized 3/8 (37.5%)</li> <li>Not Hospitalized 5/8 (62.5%)</li> </ul> <p><b>Severity of Condition:</b> NR</p> <p><b>Duration of Condition:</b> NR</p> <p><b>Comorbid Conditions:</b></p>

<p><b>IVA Score:</b> 17 (High)</p>	<p>telephone. Subjects were derived from Italian Registry of Severe A1AT deficiency. COVID-19 was diagnosed via laboratory tests for SARS-CoV-2 on nasal swabs or blood samples.</p> <p><b>Exclusion Criteria:</b> NR</p>		<p><i>Non-elective readmissions:</i> NR</p> <p><b>Comments:</b> Author's note: The survey only reached 35% of the Italian cohort with severe A1AT deficiency.</p>	<p>The one patient who died was already long-term hospitalized because of severe lung impairment before COVID-19 infection.</p> <p><b>Risk Markers:</b> NR</p> <p><b>Long-term Sequelae:</b> Non-elective readmissions: NR</p>
<p><b>Author:</b> Schneider<sup>2</sup></p> <p><b>Year:</b> 2021</p> <p><b>Data Extractor:</b> AH</p> <p><b>Reviewer:</b> DOS</p> <p><b>Study Design:</b> Cohort</p> <p><b>Study Objective:</b> To study the association between alpha-1-antitrypsin deficiency (A1AT deficiency) and SARS-CoV-2 infection.</p> <p><b>IVA Score:</b> 15 (High)</p>	<p><b>Population:</b> N = 14,393</p> <p><b>Setting:</b> Community</p> <p><b>Data Source:</b> UK Biobank and national death registries</p> <p><b>Location:</b> United Kingdom</p> <p><b>Study Dates:</b> NR – February 18, 2021</p> <p><b>Inclusion Criteria:</b> Patients recruited to a community-based cohort from 22 centers who had genotyping available on the most clinically relevant AAT variants Pi*Z (rs28929474) and Pi*S (rs17580).</p> <p><b>Exclusion Criteria:</b> NR</p>	<p><b>Medical Condition, n/N (%):</b> A1AT deficiency: 1,1670/14,393 (11.60%)</p> <p><b>Control/Comparison Group, n/N (%):</b> No A1AT deficiency: 12,723/14,393 (88.40%)</p>	<p><b>Medical Condition(s):</b> A1AT deficiency: included the most clinically relevant AAT variants Pi*Z (rs28929474) and Pi*S (rs17580)</p> <p><b>Severity Measure(s):</b> <i>Pi*MS:</i> ND <i>Pi*SS:</i> ND <i>Pi*MZ:</i> heterozygous Pi*Z genotype results in mild A1AT deficiency <i>Pi*SZ:</i> combined presence of Pi*S and Pi*Z variants <i>Pi*ZZ:</i> homozygous Pi*Z genotype, the predominant cause of severe A1AT deficiency</p> <p><b>Clinical Marker:</b> NR</p> <p><b>Outcome Definitions:</b> <i>Mortality:</i> Death by COVID-19 <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p><b>Comments:</b> None</p>	<p><b>Severe COVID-19:</b> <i>Mortality, n/N (%):</i></p> <ul style="list-style-type: none"> <li>• A1AT deficiency: 53/1,670 (3.20%)</li> <li>• No A1AT deficiency: 353/12,723 (3.00%)</li> </ul> <p><b>Severity of Condition:</b> <i>Mortality, n/N (%):</i></p> <ul style="list-style-type: none"> <li>• Pi*MS: 37/1,156 (3.20%)</li> <li>• Pi*SS: 1/28 (4.00%)</li> <li>• Pi*MZ: 14/460 (3.04%)</li> <li>• Pi*SZ: 1/23 (4.35%)</li> <li>• Pi*ZZ: 0/3 (0.00%)</li> </ul> <p><b>Duration of Condition:</b> NR</p> <p><b>Comorbid Conditions:</b> NR</p> <p><b>Risk Markers:</b> NR</p> <p><b>Long-term Sequelae:</b> NR</p>

<p><b>Author:</b> Shapira<sup>3</sup></p> <p><b>Year:</b> 2020</p> <p><b>Data Extractor:</b> AH</p> <p><b>Reviewer:</b> ES</p> <p><b>Study Design:</b> Cross-sectional ecological</p> <p><b>Study Objective:</b> To examine a possible association between the distributions of common SERPINA1 single nucleotide polymorphisms (SNPs) underlying A1AT deficiency and between COVID-19 epidemiology on a global scale.</p> <p><b>IVA Score:</b> 17 (High)</p>	<p><b>Population:</b> N = 67 countries</p> <p><b>Setting:</b> Population-level</p> <p><b>Data Source:</b></p> <ul style="list-style-type: none"> <li>• Relevant literature: 2017 National PiS &amp; PiZ allele frequencies</li> <li>• United Nations database: 2018 date for all indicators except for 2017 inbound tourism</li> <li>• The World Bank Open Data: 2018 Population size, density, male percentage, urban percentage, and age composition</li> <li>• Johns Hopkins University: 2020 National COVID-19 infection rates</li> </ul> <p><b>Location:</b> International</p> <p><b>Study Dates:</b> Up to September 7, 2020</p> <p><b>Inclusion Criteria:</b> Countries with a population &gt;1million</p> <p><b>Exclusion Criteria:</b> NR</p>	<p><b>Medical Condition, n/N (%):</b> A1AT deficiency: NR</p> <p><b>Control/Comparison Group, n/N (%):</b> NA</p>	<p><b>Medical Condition(s):</b> Alpha 1 antitrypsin (A1AT) deficiency: presence of any of the following alleles: - PiS (SERPINA1 rs17580) and PiZ (SERPINA1 rs28929474,)</p> <p><b>Severity Measure(s):</b> ND</p> <p><b>Clinical Marker:</b> ND</p> <p><b>Outcome Definitions:</b> Mortality: ND ICU admission: NR Intubation: NR Ventilation: NR Hospitalization: NR Non-elective readmissions: NR</p> <p><b>Comments:</b> None</p>	<p><b>Severe COVID-19:</b> <i>R: Pearson Correlation (r); ANCOVA (Analysis of Covariance)</i></p> <p><i>Mortality, n/N (%):</i> <i>Correlation of national rates of population adjusted COVID-19 mortality with A1AT deficiency allele frequencies. Adjusted for urbanization, age distribution, etc.</i></p> <ul style="list-style-type: none"> <li>• Pearson R=0.56, p = 0.00000087</li> </ul> <p><i>Correlation of national rates of COVID-19 mortality with A1AT deficiency allele frequencies</i></p> <ul style="list-style-type: none"> <li>• Pearson R=0.54, p = 0.00000198</li> </ul> <p><b>Severity of Condition:</b> NR</p> <p><b>Duration of Condition:</b> NR</p> <p><b>Comorbid Conditions:</b> NR</p> <p><b>Risk Markers:</b> NR</p> <p><b>Long-term Sequelae:</b> Non-elective readmissions: NR</p>
<p><b>Author:</b> Yoshikura<sup>4</sup></p> <p><b>Year:</b> 2021</p>	<p><b>Population:</b> N = 68 countries</p> <p><b>Setting:</b> NR</p>	<p><b>Medical Condition, n/N (%):</b> A1AT deficiency: NR</p>	<p><b>Medical Condition(s):</b> A1AT deficiency: Pi*S, Pi*Z, and Pi*SZ</p>	<p><b>Severe COVID-19:</b> NR</p> <p><b>Severity of Condition:</b> <i>Mortality correlation coefficient:</i></p>

<p><b>Data Extractor:</b> MM</p> <p><b>Reviewer:</b> DOS</p> <p><b>Study Design:</b> Ecological</p> <p><b>Study Objective:</b> To examine the epidemiological correlation between the COVID-19 epidemic and A1AT deficiency.</p> <p><b>IVA Score:</b> 18 (Moderate)</p>	<p><b>Data Source:</b> WHO COVID-19 situation reports, A1AT deficiency prevalence data tables published in relevant literature, Worldometer, and World Bank data</p> <p><b>Location:</b> International</p> <p><b>Study Dates:</b> January 21 – June 18, 2020</p> <p><b>Inclusion Criteria:</b> Countries for which mortality data from WHO COVID-19 situation reports and A1AT deficiency prevalence data from Blanco et al. (2017) is available.</p> <p><b>Exclusion Criteria:</b> NR</p>	<p><b>Control/Comparison Group, n/N (%):</b> No A1AT deficiency: NR</p>	<p><b>Severity Measure(s):</b> <i>A1AT deficiency PI*S:</i> frequent mutant allele and milder variant <i>A1AT deficiency PI*SZ:</i> serum level 75-150 mg/dL <i>A1AT deficiency PI*Z:</i> frequent mutant allele and most severe variant</p> <p><b>Clinical Marker:</b> NR</p> <p><b>Outcome Definitions:</b> <i>Mortality:</i> ND <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p><b>Comments:</b> None</p>	<p>PI*S</p> <ul style="list-style-type: none"> <li>All: 0.6326</li> <li>Europe &amp; America: 0.8244</li> <li>Other regions: 0.4360</li> </ul> <p>PI*SZ</p> <ul style="list-style-type: none"> <li>All: 0.8585</li> <li>Europe &amp; America: 0.8864</li> <li>Other regions: 0.0253</li> </ul> <p>PI*Z:</p> <ul style="list-style-type: none"> <li>All: 0.8713</li> <li>Europe &amp; America: 0.9503</li> <li>Other regions: 0.4360</li> </ul> <p><b>Duration of Condition:</b> NR</p> <p><b>Comorbid Conditions:</b> NR</p> <p><b>Risk Markers:</b> NR</p> <p><b>Long-term Sequelae:</b> Non-elective readmissions: NR</p>
---	--	---	---	---

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

**Table 7** Internal Validity Assessments of Extracted Studies Reporting the Association Between A1AT Deficiency and Severe COVID-19 Outcomes

Author Year		Schneider 2021 <sup>2</sup>	Shapira 2020 <sup>3</sup>	Yoshikura 2021 <sup>4</sup>
Outcome		Mortality	Mortality	Mortality
Domain	Signaling question			
Study Elements	Design appropriate to research question	1	0	0
	Well described population	1	0	1
	Well described setting	1	0	0
	Well described intervention/ exposure	1	1	0
	Well described control/ comparator	1	0	0
	Well described outcome	1	1	1
	Clear timeline of exposures/ interventions and outcomes	0	1	1
Selection Bias: Sampling	Randomization appropriately performed	0	0	0
	Allocation adequately concealed	0	0	0
	Population sampling appropriate to study design	1	1	0
Selection Bias: Attrition	Attrition not significantly different between groups	0	0	1
	Attrition <10-15% of population	0	0	1
	Attrition appropriately analyzed	0	0	1
Information Bias: Measurement and Misclassification	Measure of intervention/ exposure is valid	1	1	0
	Measure of outcome is valid	1	1	1
	Fidelity to intervention is measured	0	0	0
	Fidelity to intervention is valid	0	0	0
	Prospective study	1	1	1

	Adequately powered to detect result	0	1	0
Information Bias: Performance & Detection	Outcome assessor blinded	0	0	0
	Study participant blinded	0	0	0
	Investigator/ data analyst blinded	0	0	0
	Data collection methods described in sufficient detail	1	0	1
	Data collection methods appropriate	1	1	1
	Sufficient follow up to detect outcome	0	1	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	0	1	1
	Appropriate statistical analyses are conducted correctly	0	1	1
	Confidence interval is narrow	0	0	0
Confounding	Potential confounders identified	0	1	1
	Adjustment for confounders in study design phase	0	0	0
	Adjustment for confounders in data analysis phase	0	1	1
Reporting Bias	All pre-specified outcomes are adequately reported	1	1	1
Other Bias	No other sources of bias	1	1	1
COI	Funding sources disclosed and no obvious conflict of interest	1	1	1
<b>SCORE</b>	Threat to internal validity	15	17	18
	Low, Moderate, High	High	High	Moderate

## C. References

1. Ferrarotti I, Ottaviani S, Balderacchi AM, et al. COVID-19 infection in severe Alpha 1-antitrypsin deficiency: Looking for a rationale. Review. *Respir Med.* 07 2021;183:106440. doi:<https://dx.doi.org/10.1016/j.rmed.2021.106440>
2. Schneider CV, Strnad P. SARS-CoV-2 infection in alpha1-antitrypsin deficiency. Research Support, Non-U.S. Gov't. *Respir Med.* 08 2021;184:106466. doi:<https://dx.doi.org/10.1016/j.rmed.2021.106466>
3. Shapira G, Shomron N, Gurwitz D. Ethnic differences in alpha-1 antitrypsin deficiency allele frequencies may partially explain national differences in COVID-19 fatality rates. *Faseb J.* 11 2020;34(11):14160-14165. doi:<https://dx.doi.org/10.1096/fj.202002097>
4. Yoshikura H. Epidemiological correlation between COVID-19 epidemic and prevalence of alpha-1 antitrypsin deficiency in the world. *Glob. Apr* 30 2021;3(2):73-81. doi:<https://dx.doi.org/10.35772/ghm.2020.01068>
5. De Souza L, Nwanji V, Kaur G. An auspicious triumph of recovery from dialysis-requiring acute kidney injury in COVID-19 in a patient with chronic kidney disease, alpha-1 antitrypsin deficiency, and liver transplant: A case report. Case Reports. *Clin Nephrol.* Dec 2020;94(6):297-306. doi:<https://dx.doi.org/10.5414/CN110294>
6. Faria N, Ines Costa M, Gomes J, Sucena M. Alpha-1 antitrypsin deficiency severity and the risk of COVID-19: A Portuguese cohort. Letter. *Respir Med.* 05 2021;181:106387. doi:<https://dx.doi.org/10.1016/j.rmed.2021.106387>

## D. Abbreviations

Acronym	Full
95% CI	95% confidence interval
A1AT	Alpha-1 Antitrypsin deficiency
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
ARF	acute respiratory failure
BMI	body mass index
BPD	bronchopulmonary dysplasia
CF	cystic fibrosis
CFR	case fatality ratio
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
ECMO	extracorporeal membrane oxygenation
EHR	electronic health record

EMR	electronic medical record
ERT	evidence review team
IQR	interquartile range
GLM	generalized linear model
HR	hazard ratio
ICD10	International Classification of Diseases 10
ICS	inhaled corticosteroids
ICU	intensive care unit
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IVA	Internal validity assessments
MICU	medical intensive care unit
MR	mortality rate
ND	not defined
NR	not reviewed
OR	odds ratio
PCR	polymerase chain reaction
PECO	population, exposure, comparator, and outcomes
RR	rate ratio
RT-PCR	real time polymerase chain reaction
SNP	single nucleotide polymorphisms