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ORIGINAL RESEARCH

COVID-19 in Individuals with Severe Alpha 1-Antitrypsin Deficiency

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Background: The risk of coronavirus (COVID-19) can be affected by the presence of certain chronic conditions. It is unknown if individuals with severe hereditary alpha-1-antitrypsin deficiency (AATD) faced an increased risk of severe COVID-19 infection during the pandemic and if COPD in this population affected the risk of severe COVID-19 outcomes.

Aim: Our aim was to investigate COVID-19 outcomes in individuals with severe AATD and to identify if COPD was a risk factor for severe disease.

Methods: Between 2021–2023 we interviewed 863 individuals with severe AATD (phenotype PiZZ) included in the Swedish National AATD Registry. Details on COVID-19 outcomes were collected. Cox regression models were used to assess risk of mild and severe COVID-19 by presence of COPD.

Results: Of 863 subjects with severe AATD, 231 reported COVID-19 infection (208 mild and 23 severe COVID-19). Subjects with severe COVID-19 were older, had lower FEV_1 values, were more likely ever-smokers and had more comorbidities compared to those with mild COVID-19. Subjects with COPD had over a 5-fold increased risk of severe COVID-19 compared to those without COPD (HR 5.43 (95% CI 1.61–18.27, p=0.006). After adjusting for potential confounders including smoking habits the risk remained significant (HR 3.72 (95% CI 1.04–13.23, p=0.043)).

Conclusion: Most patients with severe AATD exhibit mild symptoms of COVID-19 infection, managing them in the community. Patients who also have COPD are at increased risk of severe COVID-19 infection.

Plain Language Summary: It is unknown if individuals with a genetic condition affecting the lungs - known as severe hereditary alpha-1 antitrypsin deficiency (AATD) were at higher risk of severe coronavirus (COVID-19) infection during the pandemic.

We interviewed 863 individuals with severe AATD between 2021-2023 and collected information on whether they had tested positive COVID-19 during the pandemic and if so, whether they needed hospital care or were able to manage this in the community. We also assessed if having chronic obstructive pulmonary disease (COPD) as well as severe AATD affected the risk of having severe COVID-19 infection.

We found that out of 863 subjects with severe AATD, 231 reported COVID-19 infection of which most reported only mild COVID-19 infection that did not require hospitalization.

Individuals with severe AATD that also had COPD reported a 5 times higher risk of severe COVID-19 - requiring hospitalization, than those individuals without COPD, which was not explained by smoking. This risk is however in line with that seen for COPD in the general population.

In summary, most individuals with severe AATD had mild symptoms of COVID-19 during the pandemic. Those that also had COPD had a higher risk of severe COVID-19, however this risk is in line with the risk that is expected for COPD patients in the population.

Keywords: alpha-1-antitrypsin deficiency, COVID-19, COPD

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Background

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel beta-coronavirus severe acute respiratory syndrome (SARS-CoV-2), has emerged as one of the most significant health challenges for humanity in recent centuries. Currently, over 760 million people have been affected, with more than 6.9 million deaths certified worldwide by the World Health Organization. Moreover, this infection has placed numerous healthcare systems on the verge of collapse, affecting even those in several developed countries.[1–3]

The disease spectrum ranges from mild symptoms or an asymptomatic presentation to the development of severe illness with a fatal outcome. In severe cases, patients experience lung damage with pronounced parenchymal changes leading to severe hypoxia. The severe lung damage, hypoxia, and multi-organ failure are attributed to virus-induced endothelial damage and the activation of the platelet and coagulation system. Following the acute phase, many patients report prolonged symptoms such as fever, fatigue, reduced physical condition, chest pains, memory disturbances, and sleep difficulties, lasting for several weeks to months. Identified risk factors for serious disease such as old age and obesity, alone cannot explain the significant variation in the severity of COVID-19 infection, indicating the presence of other crucial factors.[4]

Alpha-1-antitrypsin (AAT) is the most abundant and important serine proteinase inhibitor in human plasma. Synthesized primarily in the liver and secreted into circulation, the synthesis and plasma concentration of AAT are genetically controlled. In some phenotypes, plasma AAT concentration is reduced. In severe, hereditary AAT deficiency (phenotype PiZZ), the AAT content in plasma is only 10–20% of the normal level.[5] AAT plays a pivotal role in inactivating serine proteases, including neutrophil elastase (NE), which degrades lung tissue. TMPRSS2 (Transmembrane serine protease 2) is another crucial serine protease in viral infections, facilitating cellular entry and replication of viruses, including SARS-CoV-2.[6] Recent studies indicate that AAT can block TMPRSS2, potentially reducing virus replication and improving prognosis in COVID-19 infection.[7,8]

The number of seriously ill COVID-19 patients and mortality has been high in several European countries where AAT Deficiency (AATD) has a high prevalence.[9–11] It remains unclear whether individuals with severe hereditary AATD faced an increased risk of severe COVID-19 infection and illness. Further, it also remains unclear if pre-existing pulmonary disease such as chronic obstructive pulmonary disease (COPD) in this population affects the risk of severe COVID-19 outcomes.

Some studies have previously suggested that patients with AATD should be considered at a higher risk of developing severe COVID-19.[12–15] We hypothesized that individuals with severe AATD are likely to develop severe COVID-19 infection with a need for further hospital intervention, rather than mild self-limiting disease. We also hypothesized pre-existing pulmonary disease such as COPD would be a factor that would affect such outcomes.

The aim of this study was to investigate the outcomes of COVID-19 in individuals with severe AATD and to identify the risk factors associated with severe disease.

Methods

Study Population

The individuals with severe AATD (phenotype PiZZ) included in this study were selected from the Swedish National AATD Register, which is described in detail elsewhere.[16] The register was established in 1991 and inclusion criteria are age ⩾18 years, a diagnosis of severe AATD (phenotypes PiZZ and PiZNull, verified by isoelectric focusing) and written, informed consent to participate. The results from the clinical examination, laboratory analyses of liver function and lung function tests measured by means of spirometry, performed at the individual's local hospital or home clinic every two years, are reported to the AATD Register by the attending physician, via a questionnaire. The questionnaire also includes questions on medical diagnoses, smoking habits and tobacco consumption. In 2020, the AATD register underwent an update, facilitating the direct sending of questionnaires to individuals with AATD. These questionnaires addressed a variety of topics, including education, occupation, exposure history, smoking habits, overall health status, existing medical conditions, experienced symptoms, family history, and current medication usage.

Interviews Regarding COVID-19

Individuals with severe AATD who were included in the AATD register were contacted by the following methods: telephone-interviews, postal questionnaires to their homes, or during their out-patient visits at the Department of Respiratory Medicine, Malmö. Chest physicians (EP, HT and ET) performed the patient interviews. The interviews included the following questions: "have you ever tested positive for COVID-19 infection; and if so, which test?" (PCR (polymerase chain reaction test or antigen test)), date of symptom onset, symptoms (fever, dyspnoea, cough, phlegm, chest pain, myalgia, headache, anosmia, dysgeusia, gastrointestinal symptom and other symptoms), number of sick days, which type of care they received (primary care, emergency department visit, in-patient hospitalization), if hospitalized; the number of days spent in hospital, if intensive care unit treatment was needed, need of oxygen, non-invasive ventilation, high flow nasal catheter (HFNC), treatment with oral corticosteroids, antibiotics and anticoagulant treatment. Interviews were conducted between April 2021 and September 2023. Some patients were contacted twice.

The registry's questionnaires yielded data on the following variables: smoking habits, mode of identification, results of spirometry, and the presence of pre-existing comorbid conditions before the onset of COVID-19 infection. The specific comorbid conditions considered in this study include COPD, diabetes, liver disease and cardiovascular diseases (CVD), which encompassed hypertension, angina pectoris, myocardial infarction, and cerebrovascular disease. For the purposes of this study, severe COVID-19 disease was categorized when a patient necessitated hospital admission, while mild disease was defined when hospital admission was not required, and the patient was managed either in the community or had a self-limiting illness being managed at home.

Ethical Considerations

The Swedish National AATD Registry is approved by the Regional Ethical Review Board, Lund, Sweden and by the Swedish Data Inspection Board. The study was carried out according to the principles of the Declaration of Helsinki. The present study was approved by the Regional Ethical Review Board, Lund, Sweden and Swedish Ethical Review Authority (2014/427and 2020–03814). As a retrospective collection of fully anonymised clinical data from medical records, consent was not considered to be required.

Statistical Analyses

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corporation, Armonk, NY, USA). The χ^2-test and Fishers exact test were used to analyze categorical data. For continuous data, means with standard deviation (SD) were used when the distribution was normal. For data that did not have a normal distribution the median values were used. Comparisons of continuous variables with normal distribution were analyzed using ANOVA.

Cox regression models were run to obtain hazard ratios (HR) (with 95% confidence intervals) for mild, severe and all COVID-19 outcomes by categories of COPD diagnosis (yes/no). Time from baseline examination until start of symptoms (mild COVID-19), date of hospitalization (severe COVID-19), or to end of follow-up (1st September 2023) was used. For mild COVID-19 outcome, cases were compared to no COVID-19. For severe COVID-19 outcomes, cases were compared to a group of subjects that either had mild COVID-19 or no COVID-19. Adjustments were made for potential confounders (Model 1: age, sex, presence of comorbidity (CVD, diabetes or liver disease, Model 2: Model 1 + smoking status). Proportional hazards assumption was checked visually using Kaplan Meier plots. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Up until 1st September 2023, 1922 individuals with severe AATD were included in the Swedish national AATD Registry. There were 670 deaths before the start of the study why they were excluded from the statistical analyses. The remaining 1252 individuals were invited to the interview.

The total number of responders was 863 individuals (69%). Of these, 554 individuals (64%) were interviewed by telephone, 184 individuals (21%) answered the postal questionnaire, and 125 individuals (15%) answered the questionnaire during their outpatient visit at our department. Of the 863 responders, 218 individuals were interviewed twice. The flow of subjects through the study is illustrated in Figure 1.

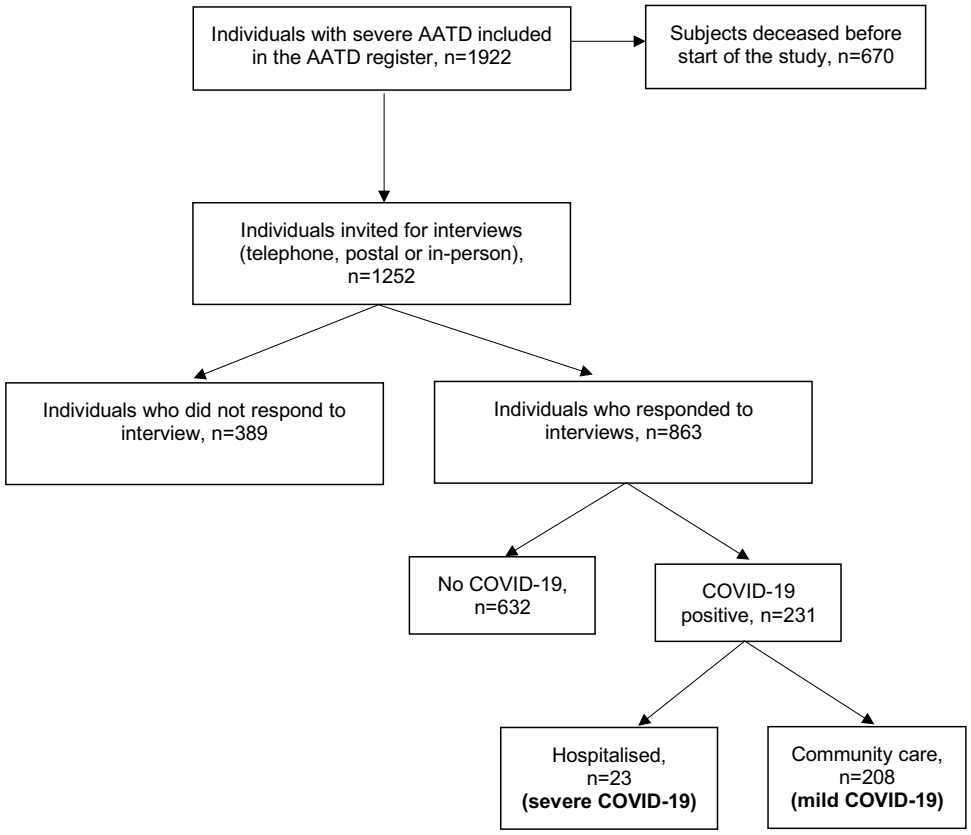

Figure 1 Flow of participants through the study.

Demographic and clinical data for individuals with severe AATD are shown in Table 1.

None of the individuals included in this study received any regular AAT augmentation therapy. Out of 863 participants, 231 individuals (27%) reported having tested positive for COVID-19 infection by PCR or antigen test. Of them, 23 (10%) were admitted to hospital and had severe COVID-19. The remaining 208 subjects (90%) hade mild disease. Of them 15 had contact with the outpatient clinic and the remaining 193 patients did not need medical contact or care.

Table 1 Demographic and Clinical Data of the Study Population

	All N=863	Tested Positive for COVID-19 N=231	No COVID-19 N=632	P value
Males, n (%)	378 (44)	103 (45)	275 (44)	0.781
Age at inclusion (years)*	42 (±17)	38 (±16)	44 (±16)	<0.001
Age at study start (years)**	55 (±4)	50 (±14)	57 (±14)	<0.001
AAT (g/L)	0.24 (±0.07)	0.23 (±0.06)	0.25 (±0.7)	0.074
Ever-smokers, n (%)	365 (42)	89 (39)	276 (44)	0.174
Pack years	9.7 (±8.8)	9.6 (±8.3)	9.8 (±8.9)	0.862
Lung transplantation, n, (%)	25 (3)	7 (3)	18 (3)	0.823

(*Continued*)

Table 1 (Continued).

	All N=863	Tested Positive for COVID-19 N=231	No COVID-19 N=632	P value
Comorbidity, n (%)				
COPD	461(53)	111 (48)	350 (55)	0.056
Liver disease	51(6)	10 (4)	41(6)	0.234
Cardiovascular disease	278 (32)	62 (27)	216 (34)	0.041
Diabetes	58 (7)	17 (7)	41(6)	0.53
FEV_1 (% predicted)	89 (±26)	92 (±23)	88 (±27)	0.195
FVC (% predicted)	102 (±22)	103 (±22)	102 (±23)	0.626
FEV_1/FVC	0.70 (±0.41)	0.71 (±0.36)	0.69 (±0.44)	0.503

Notes: Data are presented as mean (± standard deviation) unless otherwise stated. *age at inclusion i AATD registry, **age at the start of the current study in 2019.
Abbreviations: n, number; COPD, chronic obstructive pulmonary disease; L, liter; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Hospitalization (Severe COVID-19)

The median duration for hospital stay for the 23 patients who were admitted was 8 days (range 1–47 days). One of the patients with comorbidities (COPD and CVD) required long in-patient care (47 days) including treatment with HFNC and oxygen and subsequently required 6 weeks of rehabilitation. The range of the hospital stay for the remaining 22 patients who were admitted to hospital was 1–19 days. Three of the remaining 22 admitted patients were also treated with oxygen. None of the 23 admitted patients needed admission to the intensive care unit (ICU).

Outpatient Clinic or No Medical Care (Mild COVID-19)

Of the 208 patients who reported mild COVID-19, 193 (93%) experienced mild symptoms, describing them as flu-like symptoms. They were able to manage their symptoms at home without the need for medical care. Fifteen patients had contact with the primary care or the outpatient clinic and were assessed by medical personnel as stable, with no requirement for hospitalization.

COVID-Related Symptoms

The most common symptoms of COVID-19 were fever in 95 patients (41%), cough in 85 (37%), dyspnoea in 46 (20%), muscle pain in 59 (26%), headache in 57 (25%), anosmia in 30 (13%), dysgeusia in 30 (13%), gastrointestinal symptoms in 16 (7%) and fatigue in 27 (12%) patients. The mean time from symptoms onset and recovery was 12 days (range 2–89).

When severe and mild subsets of patients were compared, the patients with severe disease were older, a greater proportion of them were ever-smokers and they had lower FEV_1 values, along with a greater incidence of comorbidities (Table 2). Twenty-five patients had undergone lung transplantation before the pandemic. Of them, 7 had COVID-19 infection and 4 of these patients were hospitalized. The mean duration of hospital stay was 6 days (SD ±5). None of them needed admission to ICU.

Hazard ratios (HR) for mild and severe COVID-19 by presence of COPD are shown in Table 3.

The risk of mild COVID-19 was lower among subjects with a COPD diagnosis compared to those without COPD. This risk became non-significant after adjusting for potential confounders. However, the subjects with a COPD diagnosis had over a 5-fold increase in the risk of severe COVID-19 compared to those with no COPD (HR 5.43 (95% CI 1.61–18.27, p-0.006)). This association remained significant after adjusting for age, sex, and comorbidities (HR 4.82 (95% CI 1.35–17.18, p-0.015)). After further adjusting for smoking status (ever smokers and never smokers), the risk remained significant (HR 3.72 (95% CI 1.04–13.23, p-0.043)).

Table 2 Differential Characteristic in AATD Patients with Severe and Mild COVID-19 Infection

	All N=231	Severe COVID-19 N=23	Mild COVID-19 N=208	P value
Men, n (%)	103 (45)	13 (57)	90 (43)	0.20
Ever-smokers, n (%)	89 (39)	19 (83)	70 (34)	<0.001
BMI	25 (±4.6)	25 (±3.6)	26 (±4.7)	0.656
Age at onset (years)	52 (±11)	61 (±9)	52 (±11)	0.015
FEV_1 (% predicted)	92 (±23)	70 (±29)	94 (±20)	<0.001
FVC (% predicted)	103 (±22)	98 (±22)	103 (±22)	0.260
FEV_1/FVC	0.71 (±0.18)	0.60 (±0.20)	0.74 (±0.16)	<0.001
Lung transplant, n (%)	7 (3)	4 (17)	3 (1)	<0.001
COPD, n (%)	111 (48)	20 (87)	91 (44)	<0.001
Cardiovascular disease, n (%)	62 (27)	16 (70)	46 (22)	<0.001
Diabetes, n (%)	19 (8)	5 (22)	14 (7)	0.028
Liver disease, n (%)	10 (4)	2 (9)	8 (4)	0.330

Notes: Data are presented as mean (±standard deviation, SD) unless otherwise stated.
Abbreviations: BMI, body mass index; n, number; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease.

Table 3 Hazard Ratios for Mild and Severe COVID-19 According to Presence of COPD

		COPD Diagnosis (reference: No COPD)	
		Hazard Ratio (95% CI)	P-value
All COVID-19	Unadjusted	0.76 (0.59–0.98)	0.035
	Model 1	1.02 (0.77–1.35)	0.864
	Model 2	1.03 (0.77–1.36)	0.860
Mild COVID-19	Unadjusted	0.66 (0.50–0.86)	0.003
	Model 1	0.92 (0.69–1.24)	0.587
	Model 2	0.95 (0.70–1.27)	0.707
Severe COVID-19	Unadjusted	5.43 (1.61–18.27)	0.006
	Model 1	4.82 (1.35–17.18)	0.015
	Model 2	3.72 (1.04–13.23)	0.043

Notes: Model 1 adjustments: Age at study start, sex, comorbidities (CVD, diabetes, liver disease). Model 2 adjustments: Model 1 + smoking. All COVID outcome (n=231). Mild COVID (n=208) outcome (n=91 with COPD, 117 without COPD). Severe COVID (n=23) outcome (n=20 with COPD, 3 without COPD).
Abbreviations: HR, hazard ratio; CI, confidence interval.

Discussion

The results of this register-based study, which includes a large number of individuals with severe AATD indicate that severe AATD per se was not a risk factor for severe COVID-19 as the majority (90%) of individuals with severe AAT

deficiency who tested positive exhibited relatively mild symptoms of COVID-19, managing them at home without the need for medical care. However, we did find that individuals with severe AATD that additionally had COPD were at high risk of severe COVID-19 outcomes, such as hospitalization due to COVID-19.

To our knowledge, this study is the first to explore the outcomes of COVID-19 infection in a large cohort of individuals with severe AATD. Our results indicate that pre-existing COPD was associated with an increased risk of severe COVID-19 infection, which remained significant even after taking into account smoking habits along with other potential confounders. This seems to be in line with our understanding of COVID-19 infections in the general population, where the majority of individuals experience mild symptoms that do not require hospitalization, whereas higher risk individuals, with certain comorbidities such as COPD are at increased risk of adverse outcomes. In the general population, a fourfold increase in risk of developing severe COVID-19 has been found in subjects with pre-existing COPD.[17] In our study we also found an almost fourfold increase in risk of severe COVID-19 in subjects with COPD after adjustments. Therefore, although there is a risk of adverse COVID-19 outcomes in subjects that have severe AATD with COPD, the risk is in line with subjects with COPD from the general population and so no additional risk in AAT-deficient patients can be observed.

Throughout the COVID-19 pandemic, numerous epidemiological studies have reported a correlation between the geographic distribution of SERPINA1 allelic variants and the incidence of severe COVID-19 cases. However, confounding factors, such as differences in government interventions, rates of vaccination, socioeconomic status, and general population health have not been taken into consideration in these studies.[10–12] Observational studies have also revealed a heightened incidence of SARS-CoV-2 infection and an elevated susceptibility to symptomatic infection among individuals with severe AAT deficiency and lung disease.[13,14] An analysis conducted by the EARCO ERS Clinical Research Collaboration investigated the impact of COVID-19 in 105 patients with severe and moderate AATD (PiZZ, PiSZ, or rare variants with an equivalent serum AAT level < 60 mg/dL). The results suggested that poor outcomes were more prevalent in PiZZ individuals compared to PiSZ, although the difference was not statistically significant.[18] Furthermore, non-respiratory comorbidities exhibited a stronger correlation with poor outcomes than genotype, baseline FEV_1, or oxygen saturation levels. However, only 31% of the 105 patients that tested positive for COVID-19 needed hospitalization.[18]

Moreover, an analysis of a community-based cohort with over 500,000 participants assessing the association between AATD and COVID-19 in the United Kingdom Biobank revealed that the most common and mild AATD genotypes were not linked to increased SARS-CoV-2 infection rates or mortality. However, it is important to note that there were very few cases of severe AATD in this study.[19] A recently published study has identified mutations associated with AATD and AAT levels below 116 mg/dL as predictors associated with an increased likelihood of severe COVID-19. These observations suggest that patients with AATD should be considered at a higher risk of developing severe COVID-19.[15]

In our study, the majority of COVID-19 cases in AAT-deficient individuals were mild. One possible explanation for this is that AAT-deficient individuals were aware of their deficiency and their increased risk of COVID-19 infection, this led them to follow instructions carefully and minimize their exposure to the virus during the pandemic. Many patients had been in contact with our team and had been worried about falling ill with a severe infection. Those who were retired stayed at home, and those who worked chose to work from home when possible. We provided constant advice and written certificates to facilitate working from home in this situation. Thus, we believe awareness contributed considerably to the outcomes.

The results of our study provide valuable information and insights into outcomes related to COVID-19 in individuals with severe AATD. This is a cohort with a large number of individuals with severe AATD, in which the diagnosis was verified by Pi phenotyping in all cases. We were also able to contact/reach more than 69% of AAT-deficient individuals and many of them were interviewed twice, therefore thorough case finding has taken place in this group of subjects.

The limitations of our study include the self-reported nature of our outcomes including positive COVID-19 infection and symptoms. We also could not reach all individuals with known AATD who are included in the Swedish AATD Registry and therefore we have some missing information in approximately 31% of PiZZ individuals. No linkage with Swedish inpatient registry and death registry was done to know the more objective details about outcomes of these patients and therefore all information we obtained on outcome was subjective information directly from the patients.

Conclusion

Most patients with severe AATD exhibit mild symptoms of COVID-19 infection, managing them in the community. Patients who also have pre-existing pulmonary disease such as COPD are at increased risk of severe COVID-19 infection, independent of smoking history. However this risk is in line with that seen for COPD in other populations without AATD. Severe AATD itself does not seem to be a risk factor for more severe COVID-19 outcomes.

Abbreviations

AAT, Alpha-1-antitrypsin; AATD, Alpha-1-antitrypsin deficiency; BMI, Body mass index; CI, Confidence intervals; COPD, Chronic obstructive pulmonary disease; CVD, Cardiovascular diseases; FEV_1, Forced expiratory volume in one second; FVC, Forced vital capacity; HFNC, High flow nasal catheter; HR, Hazard ratio; ICU, Intensive care unit; PCR, Polymerase chain reaction test; TMPRSS2, Transmembrane serine protease 2.

Data Sharing Statement

Because of the sensitive nature of individual personal data and study materials, they cannot be made freely available.

Ethics Approval and Informed Consent

The Swedish National AATD Registry is approved by the Regional Ethical Review Board, Lund, Sweden and by the Swedish Data Inspection Board. The study was carried out according to the principles of the Declaration of Helsinki. The present study was approved by the Regional Ethical Review Board, Lund, Sweden and Swedish Ethical Review Authority (2014/427and 2020-03814). As a retrospective collection of fully anonymised clinical data from medical records, consent was not considered to be required.

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Disclosure

The authors report no conflicts of interest.

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