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ORIGINAL ARTICLE

Severe alpha-1-antitrypsin deficiency increases the risk of venous thromboembolism

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Abstract

Background: Severe alpha-1-antitrypsin deficiency (AATD), phenotype PiZZ, is associated with increased risk of liver disease and chronic obstructive pulmonary disease (COPD), but the risk of venous thromboembolism (VTE) is unknown. Our aim was to evaluate the risk of VTE in individuals with severe AATD compared with control subjects from the general population.

Methods: Individuals with severe AATD (n = 1577) were recruited from the Swedish national AATD register. Control subjects (n = 5969) were selected from the OLIN (Obstructive Lung Disease in Northern Sweden) studies, that include a random general population sample. Longitudinal data on VTE and diagnoses were obtained from the Swedish National Patient Registry. Associations were analyzed using multivariable Cox regression.

Results: At inclusion, 46% of the AATD individuals and 53% of the controls were never-smokers. COPD was present in 46% of the AATD individuals compared with 4% of the controls. During a median follow-up of 18 years, 116 (7%) of the AATD individuals and 89 (1%) of the control subjects developed VTE, unadjusted hazard ratio 6.5 (95% confidence interval 4.9–8.6). Risk factors for incident VTE were male gender, age, COPD, cancer, and liver disease. Adjusting for these factors, the AATD individuals had a significantly higher risk of incident VTE, adjusted hazard ratio 4.2 (95% confidence interval 2.9–6.2) as compared with the controls.

Conclusion: Subjects with severe AATD have considerably increased risk of developing VTE compared with the general population, even after accounting for risk factors. This calls for optimized risk factor management and clinical follow-up of this patient group.

KEYWORDS
alpha-1-antitrypsin deficiency, COPD, deep vein thrombosis, pulmonary embolism, venous thromboembolism

Essentials

- The risk of developing venous thromboembolism (VTE) in individuals with severe alpha-1-antitrypsin deficiency (AATD) is unknown.

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- The study was a national, longitudinal, register-based study of individuals with severe AATD (PiZZ) compared with control subjects randomly selected from the general population.
- The incidence rate of VTE per 1000 person-years was significantly higher among the individuals with severe AATD than among the controls, 6.2 (95% CI 5.1–7.4) versus 0.94 (95% CI 0.8–1.2).
- Individuals with severe AATD have increased risk of developing VTE compared with the general population, which is new, important knowledge for optimized clinical evaluation and follow-up of these patients.

1 | INTRODUCTION

Alpha-1-antitrypsin (AAT) is a glycoprotein mostly secreted by hepatocytes and inhibits a variety of serine proteinases, including neutrophil elastase.[1,2] The major function of AAT in the lung parenchyma is to protect the connective tissue from neutrophil elastase released from triggered neutrophils. Severe AAT deficiency (AATD), phenotype PiZZ, is inherited as an autosomal codominant condition and is characterized by markedly reduced AAT plasma levels, associated with increased risk of developing chronic obstructive pulmonary disease (COPD). AATD is caused by the decreased secretion from the liver because of polymerization and accumulation of the AAT molecule in hepatocytes, which increases the risk of liver disease.[1]

Other conditions associated with AATD include neutrophilic panniculitis, anti-neutrophil cytoplasmic antibody–associated vasculitis, peripheral neuropathy, cerebral or peripheral artery aneurysms, kidney disease, and metabolic alterations with decreased levels of serum triglycerides and very-low density lipoproteins.[3] However, the association between AATD and venous thromboembolism (VTE) is unknown. A few case reports have suggested an association between AATD and increased VTE risk.[4–7] We have also previously reported increased mortality from VTE in individuals with severe AATD compared with the Swedish general population.[8]

VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant health problem with an estimated annual incidence of approximately 1–2 per 1000 people in the general population.[9] Underlying etiological factors for VTE were first proposed by Rudolph Virchow in 1884 as the presence of at least one of the following three factors: vascular endothelial damage, stasis of blood flow, and hypercoagulability of blood. Over the past century, the recognition that all VTE risk factors reflect these underlying pathophysiological processes and that VTE does not usually develop in their absence has increased.[10] AATD might affect all components of Virchow's triad, including endothelial damage and hypercoagulability, and therefore may play a role in the pathogenesis of VTE. Data from a large longitudinal study of potentially increased VTE risk in AATD are lacking.

The aim of this study was to evaluate the risk of developing VTE in individuals with severe AATD compared with the general population.

2 | METHODS

2.1 | Study population and data collection

This was a national, longitudinal, register-based study of individuals with severe AATD (PiZZ) compared with control subjects randomly selected from the general population.

2.1.1 | AATD individuals

The AAT-deficient individuals were identified from the Swedish National AATD Register, which was started 1991.[11] Inclusion criteria in the register are 18 years of age or older, providing written informed consent, and having severe AATD (laboratory-confirmed PiZZ or PiZnull). The reasons for plasma protein analysis that led to the diagnosis of AATD included respiratory disease or symptoms, liver disease or symptoms, screening, and any other disease/symptoms that indicated plasma protein analysis leading to the diagnosis of AATD. After inclusion in the register, clinical examination, blood samples including liver function tests, and lung function tests were performed at the patient's home clinic/hospital, and the results were reported by the attending physician to the register by means of a questionnaire completed every 2 years.[11]

2.1.2 | Population-based controls

The controls were selected from three population-based, adult cohorts within the epidemiological research program, the Obstructive Lung disease in Northern Sweden (OLIN). These control cohorts included randomly selected individuals from the population register in the northern Sweden who were recruited in 1992 (n = 4851, aged 20–69 years), in 1996 (n = 7420, 20–70 years), and in 2006 (n = 6165, 20–69 years), and were invited to participate in postal questionnaire surveys.[12,13] The response rates were 85%, 85%, and 77%, respectively. The questionnaire included questions on smoking habits and symptoms.

To match the controls to the sex, smoking habits, and identification date of the PiZZ subjects, who had been included in the AATD register continuously since 1991, we randomly selected 2000 subjects from each of the three OLIN cohorts, a total of 6000

controls, as previously described.[14] No subject among the controls had known AATD as no subject was included in the AATD register.

2.1.3 | Smoking habits and diagnoses

At baseline (date of inclusion in the AAT register or the OLIN studies), smoking habits were categorized as never, former (quit smoking at least 12 months previously), and current smoking. Data on diagnoses of VTE, other diseases, and surgical procedures were obtained from the Swedish National Patient Register (SNPR).[15] The SNPR covers more than 99% of all hospitalizations since 1987 and about 80% of all hospital-based outpatient care since 2001 nationwide and includes information on the date of admission and discharge, the main and contributing diagnoses, as well as surgical procedures.

The International Classification of Disease (ICD) codes from SNPR have been validated by comparing registered diagnoses in SNPR with information in medical records.[15] The positive predictive values (PPVs) of SNRP diagnoses were 85%–95% for most diagnoses. The validation of ICD diagnosis codes of PE and DVT has been investigated in a large population study.[16] The PPVs for a diagnosis of PE or DVT were at 80.7% and 59.2%, respectively.

Diagnoses were coded according to the 9th (before 1996) and 10th World Health Organization ICD system.[17] ICD codes were categorized as (ICD-9; ICD-10): PE (415.1; I26) and DVT (453.40; I80); liver disease (570–573; K70–K76); COPD (490–496; J449). Cancer diagnosis was obtained from the SNPR and the Swedish Cancer Register (which include all diagnosed cancers nationwide) and were coded according to ICD-7 and ICD-10 as follows: oral cavity (140–148, C00-C14), digestive organs (150–159, C15–C26), respiratory organs (160–165, C30–C39), reproductive and genitourinary organs (170–181, C51–C68), hematological and lymphoproliferative (200–207, C81–C96), and skin (190–199, C43–C44).

2.1.4 | Surgical procedures

Data on surgical procedures were identified from the Swedish patient registry and coded using the Swedish classification of surgical procedures.[17] Surgery was categorized as major and minor according to the definition used in previous studies.[18,19] Major surgery was defined as all elective or emergency surgery that required general anesthesia lasting ≥30 minutes, including abdominal or thoracic surgery, coronary artery bypass, surgery for gynecological malignancies, and major urological surgery.

2.2 | Ethical considerations

The AAT register and the OLIN studies were approved by the Regional Ethical Review Board, Lund, Sweden; the Ethical Review Board at Umeå University; and by the Swedish Data Inspection Board. All participants provided informed written consent. The present study was approved by the Regional Ethical Review Board at Lund (Dnr 2014/427).

2.3 | Statistical analysis

Baseline data were tabulated using frequencies and percentages for categorical variables and means with standard deviation (SD) for continuous variables with normal distributions. Comparisons of continuous variables with normal distribution were analyzed using analysis of variance.

The primary study endpoint was incident VTE, defined as the date of first VTE diagnosis in people without any prior VTE diagnosis at baseline. All participants were followed from the date of inclusion in the AAT register, which was started in 1991, or OLIN studies, which were started in 1992, 1996, and 2006 to the date of first VTE diagnosis, lung transplantation, death, or study end (January 1, 2015), whichever came first.

Associations with incident VTE were analyzed using multivariable Cox regression. Estimates were expressed as hazard ratios (HR) with 95% confidence intervals (CI). To evaluate whether a relative risk was explained by differences in other factors, the models were adjusted for age, sex, smoking status, and the presence of COPD and liver disease at baseline or 12 months before inclusion. In a further step, we also adjusted for time-dependent changes in VTE risk factors during follow-up regarding liver disease, cancer, COPD, and major surgery, in addition to controlling for baseline characteristics (age, sex, and smoking habits).

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM Corp).

3 | RESULTS

Up to January 1, 2015, 1595 individuals were included in the AATD register, and 6000 control subjects were selected from the OLIN studies. We excluded subjects with incorrect Swedish personal identification number (one control), subjects who had undergone lung transplantation before inclusion (10 AATD), or who had a diagnosis of VTE before inclusion (eight AATD and 30 controls). The remaining 1577 AATD individuals and 5969 controls were included in the analyses. The enrollment flow chart is presented in Figure 1.

Baseline characteristics of the participants are shown in Table 1. The controls were significantly younger than the AATD individuals. The median (interquartile range) follow-up time was 18 (12) years overall; 12 years for the AATD individuals and 18 years for the controls. Smoking was more common among the controls than among the AATD individuals. At inclusion, COPD and liver disease were more common among the AATD individuals than among the controls, Table 1. Hepatocellular cancer was found in only two AATD individuals, and in none of the controls.

The diagnoses of importance for developing VTE during the follow-up are shown in Table 2. Occurrence of COPD and liver disease during the follow-up were significantly higher among the AATD

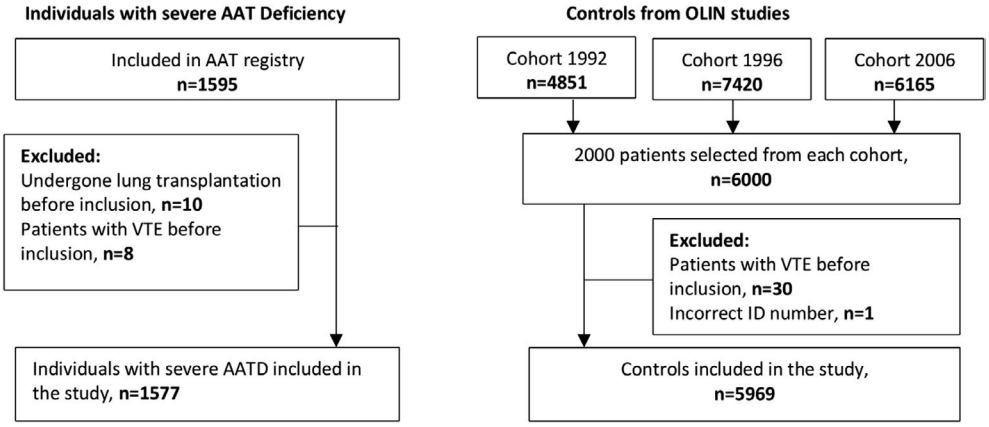

FIGURE 1 The flow-chart of the study population

TABLE 1 Characteristics of the AATD individuals and control subjects at inclusion

	AATD *N* = 1577	Controls *N* = 5969
Men, *n* (%)	773 (49)	3016 (50)
Age (y), mean ±SD	47 ± 17	45 ± 14
Smoking habits		
Current smoker, *n* (%)	130 (8)	1543 (26)
Ex-smoker, *n* (%)	718 (46)	1258 (21)
Never-smoker, *n* (%)	729 (46)	3168 (53)
Follow-up time (y), median (IQR)	12 (13)	18 (14)
COPD, *n* (%)	726 (46)	221 (4)
Liver disease, *n* (%)	56 (4)	5 (1)

Abbreviations: AATD, alpha-1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

TABLE 2 Diagnoses and surgical procedures during the follow-up in the PiZZ individuals and the controls

	AATD *N* = 1577 (%)	Controls *N* = 5969 (%)
COPD	195 (12)	167 (3)
Cancer	183 (12)	582 (10)
Liver disease	98 (6)	31 (0.5)
History of major surgery	263 (17)	1002 (17)
Venous thromboembolism	116 (7)	89 (1.4)
Pulmonary embolism Deep	87 (5)	54 (0.9)
vein thrombosis	29 (2)	35 (0.5)
Deaths, *n* (%)	525 (33)	745 (12)

Abbreviations: AATD, alpha-1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease.

individuals than among the controls, Table 2. Of the 183 AATD individuals and 582 controls who developed cancer, 28 (15%) and eights (1%) patients had hepatocellular cancer, respectively. There was no significant difference in number of major surgical procedures between the groups during follow-up, Table 2. Three individuals had undergone surgery during 3 months before the onset of VTE.

3.1 | Incidence of VTE

Development of VTE was more common among the AATD individuals than among the controls, Table 2. The number of participants who developed both PE and DVT was nine among the AATD individuals (eight of them had DVT before PE), and four among the controls (all had DVT before PE). The incidence rate of VTE per 1000 person-years was significantly higher among the AATD individuals than among the controls, 6.2 (95% CI 5.1–7.4) versus 0.94 (95% CI 0.8–1.2). The cumulative incidence of VTE in the PiZZ individuals and the controls is shown in Figure 2.

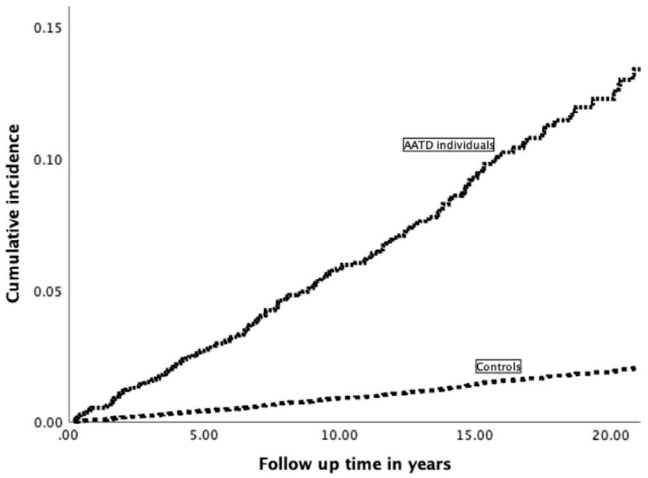

FIGURE 2 The cumulative incidence of venous thromboembolism during follow-up in the individuals with severe alpha-1-antitrypsin deficiency and in the controls

The unadjusted HR for VTE in the AATD individuals compared with the controls was 6.5 (95% CI 4.9–8.6). After adjustment for baseline factors (age, sex, smoking habits, presence of COPD and

liver disease), HR was still higher, 5.2 (95% CI 3.7–7.4). In the time-dependent multivariate analysis, AATD status, sex, age at inclusion, COPD, cancer, and liver disease were risk factors for developing VTE. Exclusion of patients with liver cancer from the statistical analysis did not influence the results. Smoking habits were not associated with an increased risk for VTE, Table 3.

4 | DISCUSSION

4.1 | Main finding

To our knowledge, this is the largest longitudinal study of individuals with severe AATD, and the first to evaluate their excess risk of developing VTE compared with the general population. The main finding is that severe AATD is associated with a highly increased risk of developing VTE compared with the general population, after controlling for risk factors. We found male sex, age, COPD, liver disease, and cancer to be risk factors for developing VTE.

Increased risk of VTE in AATD has previously been suggested in a few case reports. Several plausible biological underpinning mechanisms for this increased risk have been reported,[4–7] including unopposed proteolytic activity of plasminogen activator that could cause activation of the coagulation cascade, as well as unopposed proteinase-3 activity that could lead to a hypercoagulability. Lomas et al. gave an original description of a mechanism by which the association among AAT, thromboembolism, and other diseases and conditions could be explained.[20] They reported that the phenomenon of loop-sheet polymerization is not restricted to alpha-1-antitrypsin, which underlies AAT deficiency, but it also underlies deficiency and inactivation of other serine proteinase inhibitors (i.e., serpins) including alpha-1 antichymotrypsin, C1 inhibitor, antithrombin, and neuroserpin. This mechanism, common to several conditions, including alpha-1-antitrypsin deficiency, thus defines them as a new group, namely the serpinopathies. These conditions/disorders may reflect a gain-of-toxic-function defect resulting from the accumulation of proteins, such as in liver cirrhosis and dementia (with AAT and neuroserpin, respectively), or a loss-of-function defect, such as in emphysema, angioedema, and thrombosis (with AAT, C1 inhibitor, and antithrombin, respectively).[20]

Other studies have suggested that AAT has protective properties on the proteins in the vascular tissue, and an imbalance between neutrophil elastase and AAT levels is linked to local tissue injury, leading to many pathologies, including cancer, chronic obstructive lung disease, infectious diseases, inflammation, and thromboembolism.[21–24] Our findings show that even after controlling for important clinical characteristics, individuals with AATD have a highly increased risk of VTE compared with the general population.

We also confirmed the influence of previously known risk factors for VTE in individuals with AATD and demonstrated an influence of the most important risk factors for developing VTE, including age, cancer, and COPD.[10] These findings confirm that cancer is an independent risk factor for VTE. Accumulating evidence suggests that cancer itself induces directly or indirectly a state of hypercoagulability that is driven by the release of procoagulant factors from malignant tissue, as well as by inflammation-driven activation of endothelial cells and platelets.[25]

COPD is considered a moderate risk factor for VTE.[26] There is a high prevalence of acute PE (15%–30%) in COPD patients who have symptoms that are interpreted as acute exacerbation.[27–30] Consistent with previous reports,[31,32] we found that the COPD is associated with an increased risk of VTE.

Liver disease was associated with an almost twofold increased risk of developing VTE in our study, independent of AATD status. This extends previous studies that have found conflicting findings.[33–35] Smoking was not associated with an increased risk for developing VTE in the present study. Some prospective studies have reported smoking to be an independent risk factor for VTE,[36,37] whereas other studies have failed to detect any significant relationship between smoking and VTE.[38,39] One suggestion has been that the magnitude of the risk of smoking appears to be less robust than that of the well-established major risk factors for VTE such as cancer.[40] However, smoking is more common than the other factors and its coexistence may be associated with an additive causative effect.[40]

A strength of our study is that it pertains to a large national database of laboratory confirmed AATD (phenotype PiZZ) and is the largest longitudinal follow-up study of AATD individuals to date. The follow-up period was long, up to 23 years. The Pi phenotyping

TABLE 3 Risk factors for incident venous thromboembolism in individuals with severe AATD and controls

Variables	Adjusted HR (95% CI) for baseline factors	Adjusted HR (95% CI) for time-dependent and baseline variables
AATD versus controls	5.22 (3.67–7.42)	4.21 (2.90–6.20)
Male versus female	1.46 (1.10–1.94)	1.44 (1.10–1.91)
Age (per 1 year)	1.05 (1.04–1.06)	1.04 (1.03–1.06)
Ever- versus never-smokers	0.89 (0.67–1.19)	0.84 (0.63–1.11)
COPD, yes versus no	1.52 (1.05–2.21)	1.81 (1.22–2.68)
Liver disease yes versus no	3.65 (1.90–7.03)	1.82 (1.13–2.93)
History of major surgery	-	1.30 (0.93–1.72)
Cancer yes versus no	-	2.21 (1.62–3.01)

Abbreviations: AATD, severe alpha-1-antitrypsin deficiency; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

was confirmed at a central, certified laboratory. Because the laboratory reports personal data of all diagnosed PiZZ subjects to the AATD register, more than 95% of all identified adult PiZZ individuals in Sweden are included in the register. A further strength was the ability, using national registry data, to follow the participants longitudinally with near complete follow-up, and to compare the risk of VTE between AATD individuals and a random general population sample with known smoking habits. The Swedish personal identification number offers a unique opportunity to study diagnoses, by cross-linkage with data from mandatory Swedish national registers.

In Sweden, the SNPR covers more than 99% of all hospitalizations since 1987 and about 80% of all hospital-based outpatient care since 2001 nationwide.[15] Because VTE is always diagnosed at a hospital, all cases with VTE were with high probability included in the analyses. The validation of ICD diagnosis codes of PE and DVT has been investigated by a large population-based cohort study covering approximately two-thirds of the population older than 30 years in Northern Sweden.[16] The authors concluded, that PPV for a diagnosis of PE or DVT was 80.7% and 59.2%, respectively. For the period 2009–2014, the PPV was higher for PE (85.8%), but lower for DVT (54.1%). Misclassification occurred in 16.4% of DVT events and 1.1% of PE events. The authors concluded that the registry data on PE, especially from the most recent period, was of acceptable quality and can be considered for use in registry-based studies, whereas data on DVT was of lower quality in regard to both PPV and misclassification. However, in our study, the majority of the patients (69%) had PE as a first event and therefore the risk of misclassification of VTE is low but cannot be completely excluded. No patient was lost to follow-up.

Our study had some limitations. Body mass index could not be included in the statistical analyses because weight was not available in all study participants. Obesity may be a risk factor for VTE, even if the association of excess weight with VTE is weak.[10] Another limitation was the lack of information on other risk factors for VTE, such as immobility from protracted sitting (e.g., prolonged car or air travel) and medication (e.g., oral contraceptives), which may have influenced the results. Third, the controls were not recruited for the present study. They were identified from a separate study, in which random samples of individuals from the population register in the northern part of Sweden were selected, whereas the PiZZ subjects, who are included in the AATD register, live throughout Sweden. It is also possible, that some controls who had suffered from VTE or any other severe disease that may lead to VTE, did not answer the initial questionnaire. However, the number of controls was high, and we only analyzed occurrence of new VTE during the follow-up. Furthermore, the PiZZ subjects included in the AAT deficiency register are not a random sample of PiZZ individuals in Sweden, even if the detection rate is high in Sweden, 30%, and a high proportion of individuals were identified by screening.

In conclusion, individuals with severe AATD have a considerably increased risk of developing VTE compared with the general population. This suggests the need for optimized clinical evaluation and follow-up of this patient group. Further prospective studies are needed to explore the role of AAT in the pathogenesis of VTE and to identify the modifiable risk factors in PiZZ individuals to reduce the incidence and complication of VTE.

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CONFLICT OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the drafting as well as the content of this study.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or the analysis and interpretation of the data; all took part in drafting the article or revising it critically for important intellectual content; all gave final approval of the version to be published; and all agree to be accountable for all aspects of the work.

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