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Alpha-1-Antitrypsinmangel: Klinisches Erscheinungsbild, Risikofaktoren und Langzeitverlauf – Analyse des deutschen Registers

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Inhaltsverzeichnis

Zusammenfassung

Der Alpha-1-Antitrypsinmangel (AATM) ist eine autosomal-kodominant vererbte Erkrankung, die mit einem erhöhten Risiko für eine chronisch obstruktive Lungenerkrankung (COPD) und eine Leberzirrhose auch schon im jüngeren Lebensalter assoziiert ist (1, 2). Erstmalig beschrieben wurde die Krankheit durch Laurell und Eriksson im Jahre 1963 (1). Ein Mangel an dem in der Leber gebildeten Protein Alpha-1-Antitrypsin (AAT) führt zu einer verminderten Neutralisierung proteolytischer Enzyme, insbesondere der neutrophilen Elastase. Die Folge ist eine chronische Inflammation und Destruktion des Lungengewebes. Zudem bewirkt die Ablagerung fehlgebildeter Proteinstrukturen in den Hepatozyten eine entzündliche Reaktion mit der Folge einer Leberschädigung bis hin zur Leberzirrhose (3).

Exogene Noxen, wie Nikotinkonsum oder eine überdurchschnittliche berufliche Staubbelastung, sind bei Patienten mit AATM bedeutende Risikofaktoren für die Entwicklung einer COPD und vor allem eines Lungenemphysems schon im jungen Alter (4-6). Doch auch bei völliger Abstinenz inhalativen Rauchens oder übermäßiger Staubbelastung leiden einige Patienten mit AATM unter den Symptomen der Lungenkrankheit, wie zum Beispiel chronischem Husten und zunehmender Dyspnoe (7).

Es sind unterschiedliche Mutationen des SERPINA1 Gens bekannt, die zu verschiedenen Schweregraden eines AATM führen. Die häufigsten Genotypen, die mit deutlich verminderten Spiegeln an AAT im Blutserum assoziiert sind, sind der Genotyp Proteaseinhibitor ZZ (PiZZ) und der Genotyp Proteaseinhibitor SZ (PiSZ) (7).

Mit einer geschätzten Prävalenz in Deutschland von etwa 1:10.300 Einwohnern bei PiZZ und 1:2400 Einwohnern bei PiSZ zählt der AATM zu den seltenen genetischen Erkrankungen (8). Es wird angenommen, dass etwa 1 - 4,5 % aller COPD-Fälle durch einen PiZZ AATM verursacht werden (7). Die Entwicklung einer manifesten Leberzirrhose ist abhängig vom Lebensalter. Während im Alter unter 50 Jahren eine Leberzirrhose selten ist, konnte eine Studie an einer kleineren Patientenkohorte eine Häufigkeit von etwa 20 % bei PiZZ AATM-Patienten im Alter über 50 Jahren nachweisen (9). Oft manifestiert sich die Leberbeteiligung aber auch schon in der frühen Kindheit in Form eines prolongierten Neugeborenenikterus oder abnormen Leberenzymen (7).

Trotz Zunahme des Bewusstseins für die Erkrankung im klinischen Alltag sowie einfachen, kostengünstigen und schnellen Diagnosemöglichkeiten, ist der AATM immer noch stark unterdiagnostiziert (10). Bei allen Patienten, die trotz Abwesenheit bekannter Risikofaktoren an einer COPD oder einem Lungenemphysem leiden, sollte ein Screening auf AATM durchgeführt werden. An erster Stelle steht die laborchemische Bestimmung der AAT-Serumkonzentration. Bei einem Spiegel unterhalb des Referenzbereiches ist eine Genotypisierung des Defektes mittels Polymerase-Kettenreaktion indiziert.

Der bereits eingetretene Lungenparenchymschaden bei AATM ist irreversibel. Deshalb ist das primäre Ziel die Verlangsamung der Krankheitsprogression. Im Mittelpunkt der Behandlung steht die Entwöhnung des inhalativen Nikotinkonsums, die Vermeidung übermäßiger beruflicher Staubbelastung sowie die Prävention von Krankheitsexazerbationen (7). Neuere Studien sehen außerdem in der parenteralen Substitutionstherapie mit humanem AAT (60 mg/kg Körpergewicht wöchentlich) eine Möglichkeit den Krankheitsverlauf um ein geringes Maß zu verzögern (11). Diese Behandlungsform ist jedoch nur einem ausgewählten Patientenkollektiv mit mittelgradig eingeschränkter Lungenfunktion vorbehalten. Im Endstadium der Lungenerkrankung muss eine Lungentransplantation in Erwägung gezogen werden (7).

Eine Lebertransplantation ist die einzig bekannte Therapie bei schwerer Leberbeteiligung bei AATM (7). Im Gegensatz zur Lungentransplantation kann eine Lebertransplantation zu einer Normalisierung des AAT-Serumspiegels führen. Ob dadurch ein Fortschreiten der Lungenerkrankung gestoppt oder verlangsamt werden kann, ist jedoch fraglich (12).

Die Prognose betroffener Patienten wird maßgeblich vom Genotyp der Erkrankung sowie durch die Einhaltung einer konsequenten Nikotinkarenz bestimmt (13). Aufgrund fehlender Langzeitdaten zum Krankheitsverlauf des AATM ist eine Prognoseeinschätzung jedoch schwierig. Es ist aber allgemein akzeptiert, dass symptomatische sowie rauchende AATM-Patienten eine deutlich eingeschränkte Lebenserwartung aufweisen (14-16).

Studien an großen Patientenpopulationen sind aufgrund der erschwerten Rekrutierung von Patienten eher die Ausnahme. Deshalb spielen Registerdaten beim AATM eine entscheidende Rolle, um das Krankheitsbild, die Diagnostik sowie die therapeutischen Optionen näher zu beleuchten. Das Deutsche Register für Erwachsene mit Alpha-1-Antitrypsinmangel (AATDR) wurde 2003 gegründet und befindet sich in der Klinik für Innere Medizin V - Pneumologie, Allergologie, Beatmungs- und Umweltmedizin am Universitätsklinikum des Saarlandes in Homburg/Saar unter der Leitung von Herrn Prof. Dr. med. Dr. rer. nat. Robert Bals. Es basiert auf der Erfassung personenbezogener Krankheitsdaten (u.a. Symptomausprägung, Häufigkeit von Exazerbationen, Lungenfunktionsparametern, Lebensqualität) mit Hilfe von speziell dafür entworfenen Fragebögen.

Das Register erlaubt die Erforschung und Auswertung retrospektiver Daten von mehr als 1000 Patienten mit dieser Erkrankung. In den vergangenen drei Jahren konnten 92 weitere Patienten mit AATM für das Register rekrutiert werden, sodass die Zahl der teilnehmenden Individuen von 984 auf insgesamt 1076 gestiegen ist. Um die Wertigkeit der späteren Auswertung zu erhöhen, wurde jeder einzelne vorbestehende Datensatz in diesem Zeitraum auf Korrektheit und Vollständigkeit geprüft. Das Verschicken von Follow-up- Fragebögen an alle teilnehmenden Patienten erfolgte in den Jahren 2006, 2011 und 2015. Mithilfe der gesammelten Daten ließ sich der Verlauf der Erkrankung über einen Zeitraum von bis zu 11 Jahren erfassen.

Bei COPD-Patienten ohne AATM ist bekannt, dass das Geschlecht Einfluss auf die Krankheitspräsentation und Symptomausprägung hat (17, 18). Bei AATM-Patienten existieren jedoch

nur begrenzte Daten über geschlechterspezifische Unterschiede hinsichtlich der wichtigsten Symptome, Verlauf und Prognose. Der erste Teil dieser Arbeit bezieht sich deshalb auf die Auswertung von Querschnittsdaten und dem direkten Vergleich von mehreren Krankheitsmerkmalen zwischen Männern und Frauen mit AATM.

Die Erfassung gesundheitsbezogener Lebensqualität mit Hilfe spezieller Fragebögen ist eine weit verbreitete und anerkannte Methode zur Abschätzung der Krankheitsschwere bei Patienten mit COPD (19, 20). Im AATDR kommt der 4-seitige St. George's Respiratory Questionnaire (SGRQ) zum Einsatz, der insbesondere für Patienten mit chronischer Lungenobstruktion entwickelt wurde. Es liegen zahlreiche Studien vor, die Korrelationen zwischen schlechteren SGRQ Resultaten und erhöhter Exazerbationsrate, Nikotinkonsum, Symptomausprägung und Lungenfunktionsparametern bei Patienten mit COPD oder Patienten mit AATM nachweisen (21-24). Die meisten dieser Studien beruhen auf der Auswertung von Querschnittsdaten, nur wenige auf der Auswertung von Längsschnittdaten. In dieser Arbeit wird deshalb die Veränderung der Lebensqualität über einen mehrjährigen Zeitraum im Zusammenhang mit verschiedenen Parametern untersucht.

Im Vergleich zu den meisten anderen nationalen Registern für AATM weist das AATDR eine hohe Zahl an Patienten mit verfügbaren Follow-up-Daten auf (25, 26). In Anbetracht des begrenzten Wissenstandes über den längerfristigen Verlauf des AATM ist deshalb die Auswertung der Langzeitdaten des AATDR ein wichtiger Teil dieser Arbeit. Für Betroffene mag es von hoher Relevanz sein eine Abschätzung darüber zu erlangen, wie sich ihre Erkrankung in den nächsten Jahren entwickeln wird, wie schnell sie voranschreitet und inwiefern die Krankheitsprogression verlangsamt werden kann. Der AATM ist durch einen erhöhten jährlichen Verlust verschiedener Lungenfunktionsparameter gekennzeichnet (27). Der jährliche Verlust der Einsekundenkapazität (FEV_1) sowie der Kohlenmonoxid-Diffusionskapazität der Lunge (TLCO) sind Prädiktoren für die allgemeine Sterblichkeit. Je höher der jährliche Verlust, desto höher die Mortalität (28, 29). Um ein rasches Fortschreiten der Erkrankung zu verhindern, ist deshalb die Identifikation von Faktoren entscheidend, die zu einem erhöhten Verlust an FEV_1 oder TLCO beitragen. Frühere Studien haben bereits einige Einflussgrößen beschrieben, die mit einem erhöhten Abfall der FEV_1 bei Patienten mit AATM assoziiert sind. Dazu zählen ein verminderter Body mass index (BMI), eine verminderte Reversibilität der Bronchialobstruktion nach Bronchodilatation, eine erhöhte Exazerbationsrate sowie eine schlechtere Lebensqualität (27, 30). Ziel dieser Arbeit war es, weitere Faktoren zu identifizieren, die Einfluss auf den longitudinalen Verlauf der FEV_1 und der TLCO haben können.

Die überwiegende Mehrheit der Patienten im AATDR leidet unter AATM mit dem Genotyp PiZZ. Trotzdem sind im Register auch mehr als 100 Patienten mit dem Genotyp PiSZ erfasst, der im Vergleich zu PiZZ mit einem quantitativ weniger ausgeprägten Mangel an AAT, einem geringeren Risiko für eine Emphysementwicklung und einer besseren Prognose verbunden ist (13, 31, 32).

Inhalativer Nikotinkonsum ist einer der wichtigsten Risikofaktoren für die Entwicklung einer schwereren Krankheitsausprägung bei Patienten mit AATM (4). Da die AATM Genotypen PiZZ und

PiSZ mit unterschiedlichen Schweregraden der Erkrankung assoziiert sind, stellt sich die Frage, ob Nikotinkonsum den Krankheitsverlauf unterschiedlich stark beeinflusst. Bisher haben nur wenige Studien die Anfälligkeit der beiden Genotypen für inhalatives Rauchen im Vergleich zueinander untersucht, sodass dies ein weiteres Anliegen dieser Arbeit war.

Die Ergebnisse dieser Arbeit sind insgesamt in vier wissenschaftlichen Veröffentlichungen publiziert. In der ersten Veröffentlichung wird gezeigt, dass das Geschlecht bei den AATM-Patienten im Register nicht mit einem bestimmten Krankheitsphänotyp, der Exazerbationshäufigkeit oder der Lebensqualität assoziiert ist. Dies steht im Gegensatz zu Untersuchungen an Patienten mit COPD ohne AATM. Dort ist die Prävalenz für die Bronchitis beim weiblichen Geschlecht höher, wohingegen ein Lungenemphysem häufiger bei Männern beobachtet wird (33). Zudem weisen Frauen mit COPD ohne AATM im Vergleich zu Männern eine schlechtere Lebensqualität auf (17).

Frühere Studien an AATM-Patienten konnten bisher keinen signifikanten Zusammenhang zwischen der jährlichen Exazerbationsrate und dem jährlichen Verlust an Lebensqualität zeigen (24, 34). In unserer zweiten Veröffentlichung wird jedoch eine signifikante Korrelation zwischen der Anzahl der jährlichen Exazerbationen in der Follow-up Phase und dem jährlichen Verlust an Lebensqualität bei Patienten mit PiZZ AATM nachgewiesen. Je häufiger die Exazerbationen pro Jahr, desto stärker der Abfall des SGRQ- Scores. Es zeigt sich, dass der Verlauf der krankheitsbezogenen Lebensqualität stärker von der Exazerbationsfrequenz als von der Veränderung der FEV_1 oder der TLCO beeinflusst wird.

Ein weiteres wichtiges Ergebnis dieser Arbeit ist der Nachweis von Faktoren, die Einfluss auf den Verlust der FEV_1 und damit auf die Krankheitsprognose bei Patienten mit AATM haben. In der dritten Veröffentlichung wird in univariater und multivariater Analyse ein signifikanter Zusammenhang zwischen jährlicher Exazerbationsrate und jährlichem FEV_1-Verlust gezeigt. Damit bestätigt diese Arbeit die Ergebnisse früherer Studien (27, 30). Als eine der ersten Studien überhaupt kann diese Arbeit einen Zusammenhang zwischen der Dauer der Nikotinabstinenz und dem jährlichen FEV_1-Verlust nachweisen. Je länger AATM-Patienten nicht mehr geraucht haben, desto geringer ist die Reduktion der FEV_1 pro Jahr. Die Ergebnisse dieser Veröffentlichung unterstreichen somit die Relevanz einer strikten Nikotinkarenz bei Patienten mit AATM.

Auch die vierte Publikation befasst sich mit dem Thema Nikotinkonsum, nun aber hinsichtlich der Anfälligkeit der beiden Genotypen PiZZ und PiSZ im direkten Vergleich zueinander. Bei AATM-Patienten mit moderatem Nikotinkonsum in der Vergangenheit zeigen PiZZ Patienten im Vergleich zu PiSZ Patienten eine signifikant erhöhte Exazerbationsrate und schlechtere Lebensqualität. Dieser Unterschied relativiert sich jedoch in der Gruppe der Patienten mit starkem (Ex-) Nikotinkonsum, sodass keine signifikanten Unterschiede zwischen den beiden Genotypen mehr aufzuweisen sind. PiSZ Patienten scheinen also nur dann von einem - im Vergleich zu PiZZ Patienten - milderen Krankheitsverlauf zu profitieren, wenn ein starker Nikotinkonsum vermieden wird.

Die Ergebnisse dieser Arbeit leisten einen wichtigen Beitrag zum Verständnis des Krankheitsbildes des AATM, insbesondere zur Abschätzung des Langzeitverlaufes sowie zur Identifikation von

Risikofaktoren für eine schlechtere Krankheitsprognose. Trotzdem müssen einige Limitationen und Schwächen genannt werden: Alle erhobenen Daten beruhen auf der Selbsteinschätzung der teilnehmenden Patienten sowie auf den Angaben der behandelnden Ärzte. Zudem ist davon auszugehen, dass als Folge der Strategie der Patientenrekrutierung AATM-Patienten mit schwerer Symptomausprägung im Vergleich zur Gesamtpopulation im Register überrepräsentiert sind. Eine Übertragbarkeit der Ergebnisse auf alle Patienten mit AATM ist deshalb wohl nur eingeschränkt möglich. Kontrollierte klinische Studien sind erforderlich, um die Ergebnisse dieser Arbeit zu bestätigen.

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1.2 Abkürzungsverzeichnis

AATM	Alpha-1-Antitrypsinmangel
COPD	Chronisch obstruktive Lungenerkrankung
AAT	Alpha-1-Antitrypsin
PiZZ	Proteaseinhibitor ZZ Genotyp
PiSZ	Proteaseinhibitor SZ Genotyp
AATDR	Deutsches Register für Erwachsene mit Alpha-1-Antitrypsinmangel
FEV_1	Einsekundenkapazität
TLCO	Kohlenmonoxid-Diffusionskapazität der Lunge
BMI	Body mass index
SGRQ	St. George's Respiratory Questionnaire

2 Veröffentlichungen

2.1 Sex differences in alpha-1-antitrypsin deficiency lung disease – analysis from the German registry

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ORIGINAL RESEARCH

Sex differences in alpha-1-antitrypsin deficiency lung disease–analysis from the German registry

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Abstract

Alpha-1-antitrypsin deficiency (AATD) is a rare condition with clinical manifestations of the lung and the liver. There is evidence that the gender affects the clinical presentation of non-AATD chronic obstructive lung disease (COPD). The aim of this study was to analyze gender-dependent disease pattern in AATD-based COPD. Data from 1066 individuals from the German AATD registry were analyzed by descriptive and analytical statistics. The AAT genotypes comprised 820 individuals with PiZZ (male 56%, female 45%), 109 with PI SZ (male 55%; female 45%), and others (n = 137). A subgroup of 422 patients with available post-bronchodilator FEV_1% predicted was analyzed in detail after stratification in spirometric GOLD stages I-IV. The age of the registered individuals is 52.2 ± 13.4 years (male: 51.91 ± 13.86 years; female: 52.76 ± 13.39 years). Female patients with GOLD I-IV showed lower numbers of pack-years and lower BMI. The time between the first symptom and the establishment of the correct diagnosis was significantly longer in female (14.47 ± 16.46 years) as compared to male individuals (12.39 ± – 14.38 years, $p = 0.04$). In conclusion, the data of the registry allow to characterize the natural course of the disease and highlight differences in the clinical presentation of patients with AATD-dependent COPD.

Introduction

Patient registries represent an important tool in understanding rare diseases (1). Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder caused by mutation of the SERPINA1 gene (2). The most common mutations are the Z- and the S-mutations being involved in more than 95% of the clinical manifestations (3). The typical manifestations involve the lung and the liver. The lung may develop a specific form of chronic obstructive pulmonary disease (COPD), the liver may be affected by cirrhosis and other manifestations. The frequency of severe AATD in the general European population is about 1:5,000–15,000 (4). AATD is thus one of the more common rare genetic risk factors, nevertheless, relatively little information is known about the clinical course of the clinical consequences. A number of registries in this disease area have been established in the last decades (1, 5-11).

The German registry for individuals with AATD (gAATDR) was established in 2003 and is one of the large collection of data on AATD (7). It is associated with a detection programs that identified more than 1000 individuals with severe AATD in the past 12 years (12,13). Data from AATD registries have provided important insight into disease phenotypes. An analysis of Spanish and Italian registry patients characterized patient clusters with

Keywords: COPD, phenotype, rare disease, sex

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bronchitis, emphysema, and asthma overlap phenotype (5). FEV_1 decline was associated with the smoker status, baseline lung function, and low BMI in the Spanish registry (6). The U.S.-American databases provided early clinical data on lung function and mortality (10,14). Registry data also showed that a delay of diagnosis is also a critical issue in AATD (15). The Alpha One International Registry (AIR) is a multinational, collaborative registry with data from several thousand individuals and contributes actively to science and development of clinical trials (8).

For AATD there is only very limited data on the impact of sex on the course of disease, clinical presentation or other clinical outcomes (16, 17). In non-AATD COPD, gender is known to affect various disease characteristics. A bronchitis – airway phenotype was more frequently found in females, while the emphysema phenotype was more abundant in men. Female COPD patients express more dyspnea (18) and higher prevalence of anxiety or depression (19) and tend toward lower health-related quality of life (18). Female sex appears to be associated with increased susceptibility to smoke exposure. Women develop COPD at younger age and with lower exposure to tobacco products (20). The early-onset COPD patients were 66% women in the COPD gene study (21).

The aim of the present study was to investigate whether sex affects disease characteristics in AATD. We analyzed the baseline date of the German AATD registry and compared various disease outcomes between male and female individuals.

Methods

Structure of the German Registry for individuals with AATD

The German AATD registry (gAATDR) was established in 2003 and contributes since then to the alpha-1 international registry (AIR). The gAATDR uses the identical baseline dataset as AIR with several additional items on exacerbation frequency or comorbidity. In addition, the gAATDR comprises also a children part that is not subject of this analysis. The inclusion criterion for the registry is severe AAT deficiency, demonstrated by serum concentrations of AAT lower than 50 mg/dl with Pi ZZ or other deficient allelic variants. The questionnaires and the data storage concept were approved by the ethics committees of the Marburg University and the Landesärztekammer Saarland and the Data Safety Office of the State of Hessen (all in Germany).

Informed consent was obtained from the patients. The gAATDR is based on a questionnaire that is distributed to patients and their physicians using various pathways. The affected individuals fill in most of the questions with several items to be completed by the physician (treatment, pulmonary function). Questionnaires are sent to the registry office at the Saarland University, where data are entered in a MS Access-based database. The database is access controlled and security backups are made daily.

Data analysis

For data analysis the data until 12/2014 were used. Data were exported from the Access database into SPSS or Excel for further analysis. Data on all patients comprised N = 1066 individuals. Data analysis for the characterization of COPD patients were based on complete data sets with post-bronchodilator FEV_1% predicted with N = 422.

Statistical analysis

Categorical data are described by frequencies and percentages and analyzed using the Chi-squared test or the Fisher's exact test as appropriate. Continuous variables are displayed as mean ± SD and compared by the *t*-test, Mann–Whitney U-test or the Wilcoxon/Kruskal–Wallis test, as appropriate. Multiple groups were tested by one-way-ANOVA with Bonferroni correction for multiple comparisons as post hoc test. Values are displayed as mean plus or minus SEM. Results were considered statistically significant for p values less than 0.05. MS Access 2013 was used for data base management, IBM SPSS version 21 for statistical analysis.

Results

Demographic and clinical characteristics

We analyzed data from 1066 individuals (male 482; female 584) with a mean age of 52.2 ± 13.4 years and a BMI of 24.09 ± 5.26. Mean post-bronchodilatator FEV_1% pred. (percent of predicted) was 21.46 ± 29.36 (N = 422). The baseline characteristics are summarized in Table 1. The AAT genotypes comprised 820 individuals with PiZZ (male 56%, female 45%), 109 with PI SZ (male 55%; female 45%), and others (n = 137). The reasons for genotyping are summarized in Table 1. The delay between the first symptom and the establishment of the correct diagnosis was 13.28 ± 15.58 years (male 12.39 ± 14.38 years, female 14.47 ± 16.46 years, $p = 0.04$, *t*-test).

Sex comparisons

To analyze whether the sex affects the clinical presentation in patients with AATD-based COPD, strata were compared according to the spirometric GOLD stages I-IV. We compared age, BMI, pack-years, number of exacerbations in 2 years, and the SGRQ in all COPD stages I-IV between male and female COPD patients (Table 2). No significant differences were identified for age, number of exacerbations, or SGRQ. Female patients with GOLD I-IV showed significantly lower numbers of pack-years and lower BMI. A total number of 243 (57.72%) patients of the COPD group received augmentation therapy, 145 (58.00%) male and 98 (57.31%) female patients. All individuals were asked about the disease phenotype and indicated the presence of lung disease (81.43%), chronic bronchitis (39.87%),

Table 1. Clinical characteristics of patients of the gAATDR

	Total	Male	Female	P (male vs. female)
Subjects	1066	482	584	–
Age at entry	52.28 (13.66)	51.91 (13.86)	52.76 (13.39)	n.s.
BMI	24.09 (5.26)	24.59 (5.178)	23.50 (5.203)	n.s.
Age at diagnosis	47.32 (16.68)	46.53 (14.55)	48.34 (14.80)	n.s.
Age at symptom begin	40.78 (12.56)	40.72 (12.13)	40.89 (13.17)	n.s.
Reason for genotyping				
Lung disease	789 (72.52)	460 (80.99)	329 (74.77)	–
Liver disease	38 (3.49)	26 (5.58)	12 (2.73)	–
Other disease	27 (2.48)	15 (2.64)	12 (2.73)	–
Family screening	102 (9.38)	43 (7.57)	59 (13.41)	–
Population screening	2 (0.18)	0 (0.00)	2 (0.45)	–
Other	50 (4.60)	24 (2.23)	26 (5.91)	–

Data are presented as mean ± SD for continuous data or n (%) for categorical data.

emphysema (73.26%), asthma (15.95%), and bronchiectasis (4.78%) with no significant differences between males and females.

Discussion

The main finding of the present study was that data from a registry can be used to identify how sex may affect the clinical presentation of patients with AATD-based COPD.

The gAATDR is a comprehensive database on individuals with severe AATD. There is a dominance of the lung phenotype that is caused by the recruitment strategy and that certainly causes a bias if conclusions on the general AATD population would be made. As compared to other registries, several data items depend on patient-recoded data. In Germany, the care structure for patients with AATD is largely decentralized what makes it difficult to obtain well controlled data from specialized clinical centers. This has to be kept in mind in the analysis. As compared to the Spanish and the Italian registries (5), the gAATDR reveals comparable data for the age, the BMI, but showed higher percentages of augmented patients. The combination of national registry data allows to compare clinical data and to initiate clinical trials (8).

The focus of this analysis was to identify gender-dependent differences in the clinical presentation of AATD individuals. This research project was driven by the evidence that gender significantly affects non-AATD COPD (16, 22–24). In general COPD, bronchitis is more common in females while emphysema is more abundant in males (23). The present database did not show a clear sex-specific predominance of a phenotype, keeping in mind that this item is based on a patient reported answer.

Time to diagnosis is a critical issue in rare diseases and often delayed in AATD (15). Also in non-AATD COPD, female individuals reported delayed diagnosis

Table 2. Distribution of age, BMI, pack-years, post-bronchodilator FEV_1% pred., exacerbations/2 years, and SGRQ between male and females COPD patients stratified by spirometric COPD stages

		GOLD I N = 47 (19/28)	GOLD II N = 160 (84/77)	GOLD III N = 163 (111/52)	GOLD IV N = 51 (37/14)
Age	m	62. 58 (9.67)	52.89 (13.02)	51.73 (11.40)	49.03 (9.80)
	f	60.21 (12.82)	57.38 (10.56)	52.46 (7.62)	47.57 (8.22)
BMI $p < 0.05$	m	25.21 (3.56)	24.50 (3.69)	24.93 (4.12)	23. 02 (4.21)
	f	24.23 (5.43)	23.71 (4.01)	24.35 (6.72)	22.43 (3.03)
Pack-years $p < 0.05$	m	8.90 (9.30)	15.68 (15.84)	20.01 (18.34)	21.30 (14.93)
	f	5.71 (10.96)	10.98 (12.81)	16.21 (15.11)	14.35 (20.23)
FEV_1% post	m	96.17 (14.35)	62.46 (9.22)	39.74 (5.93)	22.37 (5.12)
	f	95.22 (14.24)	61.84 (8.55)	39.42 (5.47)	24.35 (5.25)
Exacerbations/2 years	m	0.78 (1.06)	0.66 (1.52)	0.79 (0.97)	1.47 (1.06)
	f	0.68 (0.98)	0.86 (1.07)	0.67 (1.75)	1.23 (1.36)
SGRQ	m	37.41 (17.81)	43.37 (17.69)	51.51 (17.82)	59.91 (15.37)
	f	37.37 (18.80)	49.12 (18.90)	50.94 (17.13)	55.29 (21.27)

Significances (*t*-test) refer to the combined groups GOLD I–IV. m = male, f = female.

(25). In the present analysis we found a delay until diagnosis was confirmed with a significantly larger delay in female individuals.

To analyze differences in patients with lung disease, data were stratified by post-bronchodilator FEV_1% pred. with 422 individuals available for this analysis. We found no significant differences in age, exacerbation rate, or quality of life based on the SGRQ. The numbers of pack-years and the BMI were significantly lower in female COPD patients. Exposure to tobacco is a major risk factor for the development of AATD lung disease and in non-AATD COPD women appear to be more susceptible to smoke exposure (20). Also, quality of life and the BMI are more reduced in female patients with non-AATD COPD (18, 26–28).

Access to treatment may differ between male and female patents in non-AATD COPD. Here we focused on the application of augmentation therapy, a specific treatment for AATD lung disease (29) and found no differences in the overall rate of this therapy.

Registry studies have several limitations based on their structures. The gAATDR is a patient-based database that implies a decreased data quality as compared to data collections generated in clinical trials or by data entry by health care providers. The individuals within the gAATDR are recruited through various pathways that do not represent a well-balanced distribution of phenotypes and disease manifestations. As populations based data are not available, the bias caused by the present sample procedure is difficult to estimate. Thus, it is not possible to draw conclusion on the general population or an AATD base population. In conclusion, the gAATDR provides in depth data on individuals with AATD and shows that there may be differences in clinical presentation of female and male patients with COPD. Further analysis of sex-dependent differences in disease mechanisms and clinical phenotypes will further improve diagnosis and therapy.

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Declaration of Interest Section

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The authors alone are responsible for the content and writing of the paper.

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2.2 Deterioration of quality of life is associated with the exacerbation frequency in individuals with alpha-1-antitrypsin deficiency – analysis from the German Registry

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ORIGINAL RESEARCH

Deterioration of quality of life is associated with the exacerbation frequency in individuals with alpha-1-antitrypsin deficiency – analysis from the German Registry

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Background: Alpha-1-antitrypsin deficiency (AATD) is a rare hereditary disease that is associated with a higher risk to develop chronic obstructive pulmonary disease and liver cirrhosis. Previous cross-sectional studies on AATD individuals have shown a relationship between worse St George's Respiratory Questionnaire (SGRQ) scores and elevated exacerbation rate or high cigarette consumption. There is a lack of longitudinal data on the relationship between the exacerbation rate and worsening of SGRQ during disease. The aim of this study was to provide not only cross-sectional data but also information about the deterioration in quality of life over a follow-up period up to 7 years (median follow-up period of 3.33 years).

Methods: We investigated questionnaire-based data of the German AATD registry concerning the relationship between SGRQ and exacerbation frequency, smoking history, forced expiratory volume in 1 second (FEV_1) and carbon monoxide diffusion capacity (DLCO) first in cross-sectional analysis and later in longitudinal analysis.

Results: Eight hundred sixty-eight individuals with protease inhibitor ZZ (PiZZ) genotype with an average age of 52.6±12.8 years had an SGRQ score of 45.7±20.6. SGRQ significantly correlated with the exacerbation frequency within the last 2 years (r=0.464; P<0.001), smoking history (r=0.233; P<0.001), FEV_1 (r=–0.436; P<0.001), DLCO (r=–0.333; P<0.001), and patients' age (r=0.292; P<0.001). Individuals with occupational dust exposure had significantly worse quality of life (P<0.001). Mean annual deterioration of SGRQ in all patients with available follow-up data (n=286) was 1.21±4.45 points per year. Univariate and multivariate analysis showed a significant relationship between worsening of SGRQ/year and exacerbation frequency in the follow-up period (r=0.144; P=0.015).

Conclusion: Worsening of SGRQ is associated with the exacerbation frequency in individuals with PiZZ AATD.

Keywords: SGRQ, quality of life, AATD, alpha-1-antitrypsin deficiency, COPD, exacerbations, emphysema, FEV_1

Background

Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder that leads to low circulating levels of alpha-1-antitrypsin (AAT). Affected individuals are at higher risk of developing chronic obstructive pulmonary disease (COPD) and liver cirrhosis.[1,2] The frequency of the AATD genotype protease inhibitor ZZ (PiZZ) in Western Europe is about 1:5,000–15,000.[3] Patient registries are helpful to get more insights into this orphan disease.[4] The German registry for individuals with AATD (AATDR) is a

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questionnaire-based collection of data that currently includes 1,074 individuals (12/2015).[5] It was established in 2003 and is continuously recruiting further participants. The data are self-reported with reports on pulmonary function provided by the patient's physician.

The assessment of quality of life has been established as a patient-related outcome, which correlates with airway obstruction and disease severity in COPD.[6–8] St George's Respiratory Questionnaire (SGRQ) was developed by Jones et al in the year 1991 to quantify health of patients with diseases causing chronic airflow limitation.[6] The questionnaire comprises three parts: the symptoms-, the activity- and the impacts-component. Previous studies showed a significant relationship between SGRQ-scores and exacerbation frequency, daily wheezing, sputum and dyspnea, bronchitis symptoms, 12-minute walking test and forced expiratory volume in 1 second (FEV_1) in patients with COPD.[9,10] Total SGRQ correlated significantly with prognosis and mortality in these patients.[7,8] Studies from other AATD registries have shown a relationship between worse SGRQ-scores and elevated exacerbation rate or high cigarette consumption.[11–13] Most of these studies only provided cross-sectional data about the relationship between SGRQ and exacerbation rate[11,12] except for two prior studies. Campos et al, investigated the longitudinal deterioration of SGRQ over a period of 12 months. In their study, they could not find significance between change in SGRQ and frequent exacerbations within 1 year.[13] Needham and Stockley also did not find a significant correlation between deterioration of SGRQ and exacerbations; however, they describe a greater improvement in the SGRQ symptoms-score in individuals with no or infrequent exacerbations.[14]

Our aim was not only to analyze cross-sectional data but also to investigate the influence of the exacerbation rate, the deterioration of FEV_1 (ΔFEV_1/year) and carbon monoxide diffusion capacity (ΔDLCO/year) on the change of health-related quality of life (ΔSGRQ/year) during a longer follow-up period (up to 7 years/median follow-up period of 3.33 years). The research question was whether the longitudinal deterioration of health-related quality of life is dependent on the exacerbation rate in individuals with PiZZ AATD.

To answer this question, our paper is divided into a cross-sectional (n=868) and a longitudinal follow-up analysis (n=286).

Materials and methods

Structure of the German registry for individuals with AATD

The AATDR was founded in 2003 and comprises a registry for adult patients and for individuals below 18 years of age.[5] The children's registry was excluded from the present analysis. The registry study is continuously enrolling individuals with AATD.

The inclusion criterion for the registry is severe AAT deficiency, reflected by low serum concentrations of AAT with PiZZ, protease inhibitor SZ (PiSZ) genotype or other deficient allelic variants. The questionnaires and the data storage concept were approved by the ethics committees of the Marburg University and the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (all in Germany). A declaration of informed consent was signed by all individuals.

Structure of questionnaire

The AATDR is based on a ten-page questionnaire that is sent to participants and their physicians. Exacerbations are defined as an excessive worsening of COPD symptoms with a duration of more than 2 days that required hospitalization or treatment with antibiotics or systemic corticosteroids. The questionnaire contains questions on pulmonary diseases, for example, chronic bronchitis, emphysema or pneumonia. Data on smoking history are recorded and used to calculate the cumulative nicotine consumption in pack-years. Several items of the questionnaire had to be completed by the patients' physician, for example, questions on treatment, pulmonary function, such as FEV_1, forced vital capacity (FVC) and VC and the carbon monoxide diffusion capacity (DLCO). The SGRQ was applied to measure the health-related quality of life.[6] The SGRQ consists of 50 items and three sub-scales (symptoms-, activity- and impacts-score). The scores range from 0 to 100, with higher results symbolizing worse quality of life. Questionnaires were sent to the registered patients for follow-up assessments after 2 and 7 years. The collected data were archived in an MS Access 2010 – database.

Data analysis

Data collected between 06/2004 and 12/2015 were used for the present analysis and transferred into SPSS (IBM, version 23). Patients with lung transplantation or lung volume reduction in the follow-up period were excluded from the longitudinal analysis. We analyzed data on at least one follow-up survey for 286 individuals over a period of ~2 years. Furthermore, data were available for a second follow-up survey after ~7 years for 90 individuals. In individuals with more than one follow-up survey, we averaged the available values. The follow-up period differed in some cases by several months.

Data sets are not totally complete because questionnaires were not always perfectly answered. Figure 1 shows the study

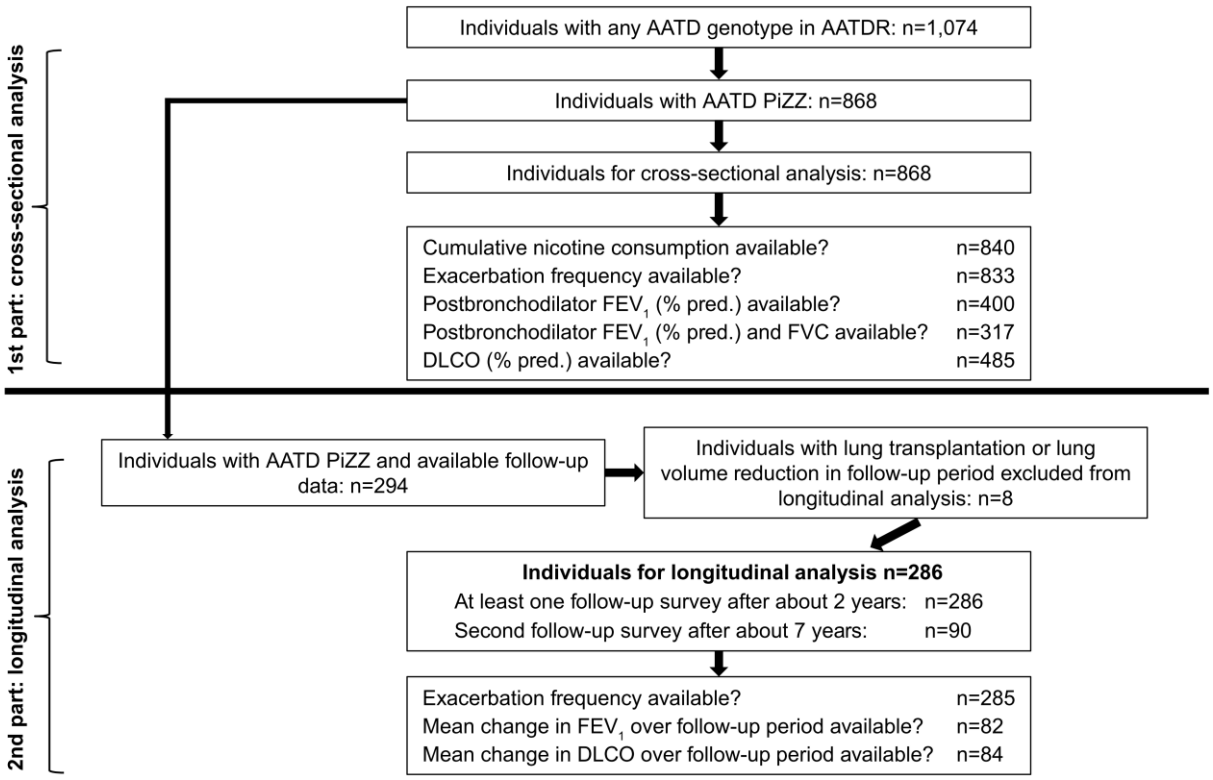

Figure 1 Flow chart showing study enrollment process.
Abbreviations: AATDR, German alpha-1-antitrypsin deficiency registry; AATD, alpha-1-antitrypsin deficiency; % pred., % of the predicted normal value; DLCO, carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PiZZ, protease inhibitor ZZ genotype.

enrollment process and the numbers of valid data for the investigated variables. For the longitudinal analysis, changes over time in FEV_1, DLCO and SGRQ were standardized by calculating the change in mL, mmol/min/kPa and score per 12 months.

Statistical analysis

Continuous variables were expressed as means ± standard deviation. The mean values of continuous variables in different groups were compared by independent samples *t*-test or Kruskal–Wallis test/one-way analysis of variance. The correlations between continuous variables were verified by multivariate linear regression models as sensitivity analysis. Due to multicollinearity between most of the variables in the multivariate regression analysis, we could not include all variables in a common model. Therefore, univariate results were analyzed by different models, including only a number of potential confounders (Tables S1–S5). In addition to the two-tailed significance, we specified the estimated effect of respective regression coefficients (β) and the 95% confidence interval. Categorical data are shown by frequencies and percentages. Statistical significance was considered for two-sided *P*-values <0.05. Our analysis was performed by IBM SPSS version 23.

Ethics approval and consent to participate

The research on the registry data including the questionnaires and the data storage concept and the publication of the data were approved by the ethical committees of the Marburg University and the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (all in Germany). A declaration of informed consent was signed by all participating individuals.

Results

Characteristics of patients

In December 2015, 1,074 AATD individuals with PiZZ, PiSZ and other deficient alleles were registered in the AATDR. We analyzed the data of 868 PiZZ AATD subjects (male n=490; female n=378). About three quarters of analyzed individuals had a history of smoking; however, most of them had quit smoking before being registered. The most common reason for diagnosis was pulmonary disorder followed by family screening. Most patients reported that they suffered from pulmonary disease, most frequently from emphysema and chronic bronchitis. Detailed baseline characteristics are summarized in Table 1.

Table 1 Baseline characteristics of patients (n=868)

Variables	Mean (SD)/n (%)
Age (years)	52.6 (12.8)
Sex (male)	490 (56.5%)
BMI (kg/m²)	24.3 (4.6)
Nicotine consumption	
Never smokers	222 (25.7%)
Former smokers	617 (71.5%)
Current smokers	24 (2.8%)
Pack-years	15.8 (16.4)/ Md: 13.5 (IQR: 0.0–24.0)
Age diagnosis (years)	47.4 (14.1)
Reason for diagnosis	
Pulmonary disease	688 (80.8%)
Liver disease	29 (3.4%)
Other disease	24 (2.8%)
Family screening	69 (8.1%)
Population screening	2 (0.2%)
Other reason	40 (4.7%)
Clinical presentation	
Pulmonary disease	775 (89.5%)
Chronic bronchitis	403 (46.4%)
Emphysema	713 (82.1%)
Asthma bronchiale	147 (16.9%)
Bronchiectasis	45 (5.2%)
Others	56 (8.7%)
Baseline FEV_1 (mL) predilatation	1,757 (930)
Baseline FEV_1 (%) predilatation	54.2 (26.4)
Baseline FEV_1 (mL) postdilatation	1,568 (683)
Baseline FEV_1 (%) postdilatation	48.4 (19.3)
Baseline FVC (mL)	3,024 (1096)
Baseline FVC (%)	76.0 (21.6)
Baseline FEV_1/FVC ratio	0.53 (0.15)
Baseline DLCO (mmol/min/kPa)	5.00 (2.47)
Baseline DLCO (%)	51.1 (22.5)
Therapy	
Bronchodilators	733 (85.2%)
LTOT	185 (21.7%)
Augmentation therapy	470 (55.0%)
Baseline quality of life (SGRQ)	
Total-score	45.72 (20.58)
Symptoms-score	54.04 (23.37)
Activity-score	56.67 (24.24)
Impacts-score	36.12 (21.39)

Abbreviations: BMI, body mass index; DLCO, carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LTOT, long term oxygen therapy; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; Md, median; IQR, interquartile range.

Increased age correlates with worse quality of life (cross-sectional analysis)

We found a significant relationship between age and SGRQ total-score (r=0.29; $P<0.001$) (and respectively to each SGRQ sub-score, all $P<0.001$; Table 2). We further confirmed a significant relationship in multivariate regression analysis, adjusted for sex, nicotine consumption, exposure of occupational dust and augmentation therapy ($P<0.001$; Table S1).

Table 2 Pearson correlations between investigated variables and SGRQ scores

Variables	SGRQ sub-score	Correlation coefficient, *r*	*P*-value
Age (n=868)	Total-score	0.292	<0.001
	Symptoms-score	0.203	<0.001
	Activity-score	0.333	<0.001
	Impacts-score	0.246	<0.001
Nicotine consumption (pack-years) (n=840)	Total-score	0.233	<0.001
	Symptoms-score	0.218	<0.001
	Activity-score	0.281	<0.001
	Impacts-score	0.177	<0.001
Exacerbation rate within the last 2 years (n=833)	Total-score	0.464	<0.001
	Symptoms-score	0.442	<0.001
	Activity-score	0.403	<0.001
	Impacts-score	0.445	<0.001
Postbronchodilator FEV_1 % pred. (n=400)	Total-score	−0.436	<0.001
	Symptoms-score	−0.309	<0.001
	Activity-score	−0.490	<0.001
	Impacts-score	−0.365	<0.001
DLCO % pred. (n=485)	Total-score	−0.333	<0.001
	Symptoms-score	−0.210	<0.001
	Activity-score	−0.405	<0.001
	Impacts-score	−0.267	<0.001

Notes: Any correlations are significantly different from zero with two-sided $P<0.001$. All analyzed variables correlate significantly with SGRQ total-score and the sub-scores.

Abbreviations: DLCO, carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; % pred., % of the predicted normal value.

Positive association between inhaled exposure (nicotine consumption and occupational dust exposure) and SGRQ (cross-sectional analysis)

Correlation analysis between SGRQ score and smoking history (pack-years) showed significant positive association in all sub-scores of SGRQ in a cross-sectional approach ($P<0.001$; Table 2; n=840). The adjusted values in multivariate analysis (Table S1; for sex, age, exposure of occupational dust and augmentation therapy) showed in some parts even higher regression coefficients in total-, symptoms-, activity- and impacts-score (β=0.24; β=0.20; β=0.30; β=0.17; all $P<0.001$). Patients who reported an occupational dust exposure (n=335) had significantly higher SGRQ scores as compared to patients without exposure (all $P<0.001$; Table 3).

Worse SGRQ is associated with the exacerbation frequency (cross-sectional analysis)

The SGRQ total-score just as the sub-scales (symptoms-, activity- and impacts-score showed a correlation with the

Table 3 SGRQ scores according to occupational dust exposure

Variables	Occupational dust exposure		*P*-value
	No (n=533)	Yes (n=335)	
	Mean (SD)	Mean (SD)	
SGRQ			
Total-score	42.91 (20.93)	50.01 (19.29)	<0.001
Symptoms-score	51.14 (23.71)	58.57 (22.12)	<0.001
Activity-score	53.32 (25.04)	61.82 (22.01)	<0.001
Impacts-score	33.02 (21.32)	40.98 (20.62)	<0.001

Notes: Any group comparisons are significant with two-sided $P<0.001$ (independent samples *t*-test). Individuals with occupational dust exposure have significantly worse SGRQ scores.
Abbreviations: SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

exacerbation rate within the last 2 years (all $P<0.001$; Figure 2; Table 2; n=833). Multivariate regression analysis (including sex, augmentation therapy and occupational dust exposure) confirmed the significant associations (total-score [β=0.41; $P<0.001$]; symptoms-score [β=0.41; $P<0.001$]; activity-score [β=0.34; $P<0.001$]; impacts-score [β=0.40; $P<0.001$]) (Table S2). SGRQ total-score correlated with the use of systemic corticosteroids (r=0.480; $P<0.001$), the increase of current medication (r=0.469; $P<0.001$), the need of antibiotics (r=0.466; $P<0.001$) and the hospitalization rate (r=0.455; $P<0.001$). Multivariate regression evaluation (adjusted for sex, augmentation therapy and occupational dust exposure) confirmed significance for the use of systemic corticosteroids, the increase of current medication, the need of antibiotics and the hospitalization rate (β=0.40; β=0.40; β=0.40; β=0.38; all $P<0.001$).

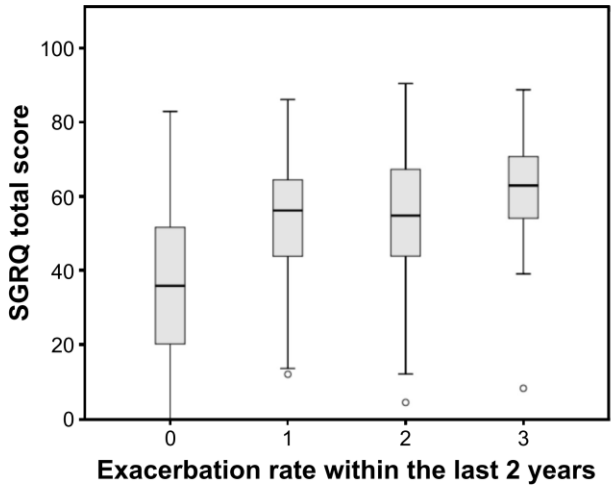

Figure 2 Worse SGRQ total-score is associated with frequent exacerbations within the last 2 years in univariate analysis.
Note: n=739.
Abbreviation: SGRQ, St George's Respiratory Questionnaire.

FEV_1 and diffusion capacity (DLCO) correlate significantly with SGRQ (cross-sectional analysis)

Low baseline bronchodilator FEV_1 % of predicted (% pred.) (available in n=400 individuals) is associated with worse quality of life total-, symptoms-, activity- and impacts-scores (all $P<0.001$) (Table 2; Figure 3). The correlation with SGRQ activity-score was stronger as compared to SGRQ total-score. Here, multivariate linear regression confirmed significance between low FEV_1 and SGRQ total-score (including sex, augmentation therapy and occupational dust exposure) (β=–0.41; $P<0.001$) (Table S3). The relationship between baseline diffusion capacity (DLCO % pred.) (available in n=485 individuals) and health-related quality of life (including sub-scales symptoms-, activity- and impacts-scores) was significant in multivariate analysis adjusted for sex, augmentation therapy and occupational dust exposure (β=–0.30; $P<0.001$) (Table S4). Individuals with available postbronchodilator FEV_1 and FVC (n=317) were classified into COPD severity levels: Global Initiative for Chronic Obstructive Lung Disease (GOLD) I (3.1%), GOLD II (29.6%), GOLD III (40.4%), GOLD IV (15.8%) and non-COPD (11.0%). The mean values of SGRQ scores were stratified according to the FEV_1-based GOLD classification (Figure 4; Table 4). The SGRQ total-score differed significantly between GOLD I–IV ($P<0.001$). In summary, patients with lower DLCO and FEV_1 or more severe spirometric GOLD stage showed higher SGRQ scores.

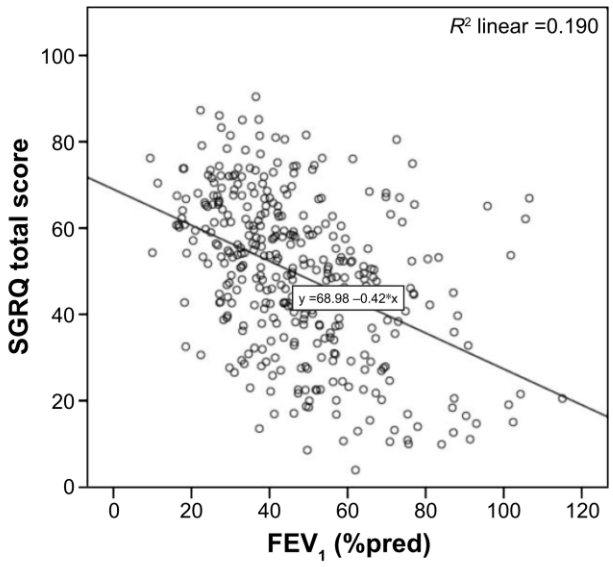

Figure 3 Scatterplot showing Pearson correlation between lung function (FEV_1 % pred.) and SGRQ total-score (univariate regression analysis) (r=–0.436; $P<0.001$).
Note: n=364.
Abbreviations: FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; % pred., % of the predicted normal value.

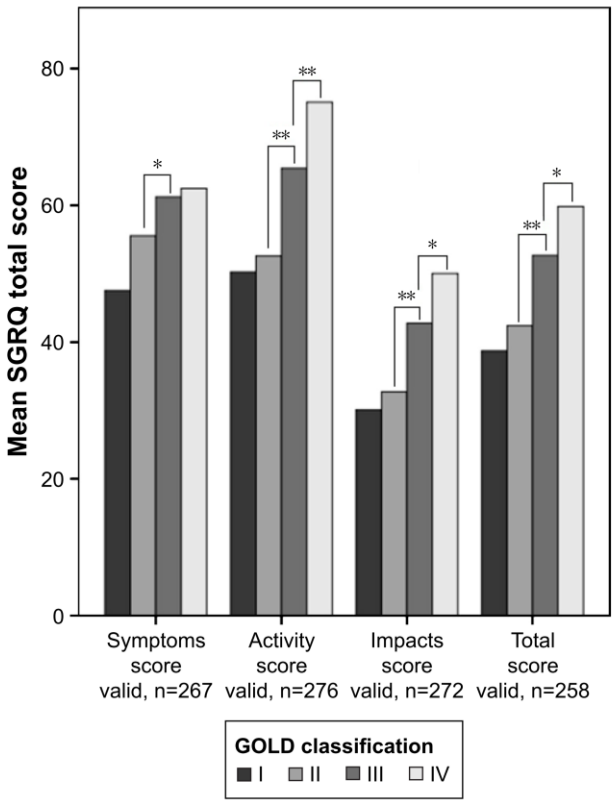

Figure 4 Mean SGRQ scores sorted by COPD GOLD classification (inter-group comparison by independent samples *t*-test).
Notes: *$P<0.05$; **$P<0.001$.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SGRQ, St George's Respiratory Questionnaire.

Individuals on augmentation therapy have worse SGRQ (cross-sectional analysis)

Individuals who reported an AAT augmentation therapy had significantly worse SGRQ total-, symptoms-, activity- and impacts-scores at baseline (all $P<0.001$) compared with subjects without this therapy (Table 5). Significant lower FEV_1 and DLCO values could be demonstrated for subjects receiving augmentation therapy (all $P<0.001$).

Deterioration of SGRQ in follow-up period correlates with exacerbation rate (longitudinal analysis)

In a next step, we analyzed the longitudinal data from follow-up surveys to identify the factors that are associated with changes of SGRQ score. The mean annual deterioration of quality of life in all patients with available follow-up data (n=286) was expressed by an increase of SGRQ score (1.21±4.45 points/year). In univariate analysis, we found significant relationship between the change of SGRQ score per year and the annual frequency of exacerbations in the follow-up period (r=0.144; P=0.015) (n=285). We confirmed this significant relationship in multivariate analysis adjusted for sex, age, augmentation therapy and occupational dust exposure (β=0.15; P=0.011) (Table S5).

Two hundred eighty-six individuals were divided into quartiles. Individuals in quartile I had low SGRQ rise or even loss of SGRQ score, patients in quartile IV had strong SGRQ rise within the follow-up period. Significant differences could be shown between quartiles of SGRQ total-score. Patients in the lowest quartile demonstrated lower exacerbation rate within the follow-up period than individuals in the top quartile (P=0.022). Significances between quartiles I and IV were also found for the need of corticosteroids (P=0.013), the increase of current medication (P=0.019) and the frequency of hospitalization (P=0.035). In inter-group comparison of all quartiles (I–IV), patients with higher deterioration in SGRQ score reported more often an increase of medication (P=0.035) and more frequent hospitalizations (P=0.036), while the need for corticosteroids (P=0.077) and antibiotics (P=0.394) only showed a trend. No significant correlations were found between the mean loss of FEV_1 (mL/year) or DLCO (mmol/min/kPa/year) and the mean increase of SGRQ scores per year (n=82 individuals with available postbronchodilator FEV_1 follow-up data; n=84 individuals with available DLCO follow-up data).

Table 4 Mean SGRQ scores sorted by COPD GOLD classification

Variables	GOLD				*P*-value	
	I (n=10)	II (n=94)	III (n=128)	IV (n=50)		Non-COPD (n=35)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)
SGRQ						
Total-score	38.72 (19.72)	42.41 (16.40)	52.68 (17.15)	59.82 (12.29)	<0.001	37.55 (21.47)
Symptoms-score	44.65 (23.18)	55.65 (19.84)	61.26 (20.84)	62.94 (17.40)	0.019	43.82 (24.22)
Activity-score	48.98 (20.87)	52.50 (19.01)	65.50 (17.27)	75.43 (12.37)	<0.001	45.71 (25.81)
Impacts-score	29.01 (18.35)	32.40 (19.22)	42.88 (19.60)	50.04 (15.45)	<0.001	30.15 (22.11)

Note: n=317 individuals with available postbronchodilator FEV_1 and FVC were analyzed by independent samples Kruskal–Wallis test.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Table 5 Characteristics of individuals with and without augmentation therapy

Variables	Augmentation therapy started?		*P*-value
	No (n=385)	Yes (n=470)	
	Mean (SD)	Mean (SD)	
SGRQ			
Total-score (n=761)	38.56 (22.10)	51.52 (17.30)	<0.001
Symptoms-score (n=809)	48.19 (25.08)	58.89 (20.70)	<0.001
Activity-score (n=815)	47.72 (27.04)	63.90 (18.82)	<0.001
Impacts-score (n=806)	29.53 (21.82)	41.48 (19.56)	<0.001
FEV_1 (mL) (n=407)	1.77 (0.80)	1.43 (0.55)	<0.001
FEV_1 (% pred.) (n=395)	54.52 (22.96)	44.37 (15.35)	<0.001
DLCO (mmol/min/kPa) (n=478)	5.52 (2.76)	4.58 (2.15)	<0.001
DLCO (% pred.) (n=479)	56.38 (24.28)	47.02 (20.16)	<0.001

Note: Subjects with augmentation therapy have significantly worse SGRQ scores, FEV_1 and DLCO in independent samples *t*-test.
Abbreviations: DLCO, carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; % pred., % of the predicted normal value.

These data are summarized in Table 6. Taken together, worsening of quality of life is associated with frequent exacerbations in the follow-up period.

Discussion

The main finding of this study was a significant relationship between the longitudinal deterioration of health-related quality of life and the annual frequency of self-reported exacerbations in individuals with severe AATD. Moreover, the cross-sectional analysis revealed significant correlations between baseline SGRQ and smoking history, the rate of moderate and severe exacerbations, postbronchodilator FEV_1 and DLCO. Most of the correlations in cross-sectional and longitudinal results were weak but significant. The study not only considered symptomatic AATD individuals but also included asymptomatic individuals with PiZZ who were diagnosed by family screening or incidental finding.

We provided longitudinal data of up to 7 years (median follow-up period of 3.33 years) and our results suggest that worsening of SGRQ is significantly associated with an elevated exacerbation rate. Previous longitudinal studies could not find a significant relationship between the deterioration of SGRQ total-score and the exacerbation frequency.[13,14]

Patient-reported outcomes, such as the assessment of health-related quality of life are increasingly recognized as important instruments in the evaluation of COPD patients.[15] It has been shown that they predict prognosis and can be used to evaluate clinical severity.[6–8] In COPD, numerous studies showed correlations between SGRQ-scores and exacerbation frequency, daily wheezing, sputum and dyspnea,

Table 6 Characteristics of follow-up SGRQ quartiles were analyzed by independent samples Kruskal–Wallis test (inter-group comparison QI–QIV) and by independent samples *t*-test (inter-group comparison QI vs QIV)

Variables	Quartiles: annual increase in SGRQ total-score (n=286)				*P*-value inter-group comparison QI–QIV	*P*-value inter-group comparison QI vs QIV
	QI (low), mean Δ SGRQ/year (SD) =−3.94 (2.83)	QII, mean Δ SGRQ/year (SD) =0.15 (0.56)	QIII, mean Δ SGRQ/year (SD) =2.07 (0.53)	QIV (high), mean Δ SGRQ/year (SD) =6.57 (3.62)		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Clinical presentation within follow-up period						
Exacerbation rate/year (n=285)	0.84 (0.82)	0.93 (0.97)	0.84 (0.94)	1.32 (1.16)	0.054	0.022
Use of corticosteroids/year (n=274)	0.59 (0.82)	0.67 (0.78)	0.71 (0.92)	1.08 (1.10)	0.077	0.013
Need of increase of medication/year (n=264)	0.62 (0.97)	0.50 (0.66)	0.59 (0.85)	1.00 (1.05)	0.035	0.019
Need of antibiotics/year (n=284)	0.82 (0.94)	0.86 (0.91)	0.83 (0.97)	1.13 (1.08)	0.394	0.144
Need of hospitalization/year (n=258)	0.34 (0.51)	0.27 (0.46)	0.39 (0.66)	0.69 (0.81)	0.036	0.035
Mean change in FEV_1 (mL/year) over follow-up period (n=82)	−126.89 (173.60)	−43.37 (81.47)	−0.55 (287.92)	−99.19 (154.59)	0.413	0.514
Mean change in DLCO (mmol/min/kPa/year) over follow-up period (n=84)	0.01 (0.72)	−0.15 (1.10)	−0.26 (0.35)	−0.26 (0.66)	0.266	0.236

Note: Subjects in quartile IV have significantly more exacerbations in comparison to subjects in quartile I.
Abbreviations: DLCO, carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

bronchitis symptoms, BODE index, 12-minute walking test and FEV_1.[9,10,16]

The results confirm other cross-sectional studies on AATD individuals that demonstrated the impact of exacerbations, lower FEV_1 and DLCO and smoking history on the SGRQ.[11,12,17]

Detailed analysis showed that SGRQ sub-scores are differentially altered. The exacerbation rate had strong influence on SGRQ impacts-score, which is related to the disease's impact on employment and daily life.[6] In contrast, nicotine consumption was most strongly associated with SGRQ activity-score. Current or former smokers may be more affected by breathlessness and restriction in physical activities.

High levels of occupational dust exposure are associated with an increased risk of more severe GOLD–COPD stages.[18] Our results showed significantly worse SGRQ in individuals with occupational dust exposure compared with unexposed individuals, underlining the importance of work-related exposure.

In accordance with studies on the Canadian AATD registry[12] patients receiving augmentation therapy had worse quality of life, FEV_1 % pred. and DLCO % pred. Augmentation therapy seems to be associated with an increased disease severity and more impaired lung function.

In the longitudinal analysis of this study, we evaluated the data of 286 individuals. However, there was a loss of 582 individuals for the follow-up assessments. Nevertheless, these individuals did not show significantly worse FEV_1, DLCO and SGRQ at baseline compared with subjects with available follow-up data. This study shows a mean annual deterioration of SGRQ score of ~1.2 units in the whole population. In non-AATD COPD, two studies reported a deterioration of ~0.06 units per year or even an improvement.[8,19] The patients in these two studies were older than in this analysis. Previous investigations on AATD individuals reported an annual worsening of SGRQ of ~1.05 points.[20] A change in SGRQ score of 4 units is regarded as clinically significant.[21] Therefore, we divided the individuals into quartiles of ΔSGRQ total-score/year in our longitudinal analysis. The quartile with the highest worsening of SGRQ (QIV) showed a clear significant mean deterioration of 6.57 units/year. Individuals with the highest deterioration of SGRQ (QIV) showed a significantly higher rate of exacerbations compared with individuals with lower deterioration or even improvement of SGRQ (QI). This concurs with the results of the study by Needham and Stockley.[14] Furthermore, in our study, the number of exacerbations in the follow-up period correlates significantly with a stronger annual impairment of quality of life. In contrast to Needham and Stockley, we found significance for the correlation in the univariate analysis and in the multivariate regression model.

Next, we analyzed the relationship between ΔSGRQ total-score/year and the decline of FEV_1 and DLCO in our longitudinal analysis. The correlation analysis as well as the comparison between high and low worsening quartiles of SGRQ (QIV vs QI) showed no significance.

We conclude that the change in health-related quality of life is more dependent on the exacerbation frequency than on the decline of FEV_1 and DLCO.

This study has some limitations: the findings might not be representative for all individuals with AATD because individuals with more severe manifestations or increased burden of symptoms might be overrepresented. As the data depend largely on self-reported information (eg, exacerbations and lung function data), the quality of these data is likely less as compared to well-controlled clinical trials. Nevertheless, our results are premised on a large study group and a long period of observation (up to 7 years).

Conclusion

The annual worsening of health-related quality of life, assessed by the SGRQ, is significantly associated with the frequency of exacerbations in individuals with PiZZ AATD (symptomatic and asymptomatic subjects) in cross-sectional and longitudinal analysis.

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Availability of data and materials: The data sets of the AATDR are located at the Department of Internal Medicine V – Pulmonology, Allergology, Intensive Care Medicine, Saarland University Hospital, Homburg, Germany and are available from the corresponding author on reasonable request.

Author contributions

NB, PML, CV, RB, and SF contributed to conception of the study, patient recruitment and original data collection and interpretation. MS contributed to the patient recruitment.

SW supported the statistical analysis. The authors alone are responsible for the content and the writing of the paper. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

RB, SF and CV have obtained research support and travel sponsoring from Talecris/Grifols and CSL Behring. CV has received honoraria for speaking engagements and for chairing a research prize committee from Talecris/Grifols. PML has received speaker fees from Talecris/Grifols. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Linear multivariate regression analysis: association between SGRQ total-score and age and nicotine consumption adjusted for sex, augmentation therapy and occupational dust exposure

Variable	Unstandardized coefficient, B	Standardized coefficient, β	95% CI	*P*-value
Age (years)	0.50	0.30	0.39 to 0.61	<0.001
Sex, female	2.06	0.05	–0.65 to 4.78	0.136
Nicotine consumption (pack-years)	0.29	0.24	0.21 to 0.37	<0.001
Augmentation therapy	10.59	0.26	7.95 to 13.22	<0.001
Occupational dust exposure	6.94	0.17	4.17 to 9.71	<0.001
Dependent variable: SGRQ total-score				

Abbreviations: CI, confidence interval; SGRQ, St George's Respiratory Questionnaire.

Table S2 Linear multivariate regression analysis: association between SGRQ total-score and exacerbation frequency adjusted for sex, augmentation therapy and occupational dust exposure

Variables	Unstandardized coefficient, B	Standardized coefficient, β	95% CI	*P*-value
Exacerbation frequency	8.09	0.41	6.86 to 9.31	<0.001
Sex, female	0.29	0.01	–2.41 to 2.98	0.834
Augmentation therapy	10.04	0.24	7.44 to 12.64	<0.001
Occupational dust exposure	5.88	0.14	3.16 to 8.61	<0.001
Dependent variable: SGRQ total-score				

Abbreviations: CI, confidence interval; SGRQ, St George's Respiratory Questionnaire.

Table S3 Linear multivariate regression analysis: association between SGRQ total-score and FEV_1 (% pred.) adjusted for sex, augmentation therapy and occupational dust exposure

Variable	Unstandardized coefficient, B	Standardized coefficient, β	95% CI	*P*-value
FEV_1 (% pred.)	–0.39	–0.41	–0.48 to –0.30	<0.001
Sex, female	3.50	0.09	–0.04 to 7.05	0.053
Augmentation therapy	2.77	0.07	–0.80 to 6.34	0.128
Occupational dust exposure	5.50	0.15	1.96 to 9.04	0.002
Dependent variable: SGRQ total-score				

Abbreviations: CI, confidence intervals; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; % pred., % of the predicted normal value.

Table S4 Linear multivariate regression analysis: association between SGRQ total-score and DLCO (% pred.) adjusted for sex, augmentation therapy and occupational dust exposure

Variable	Unstandardized coefficient, B	Standardized coefficient, β	95% CI	*P*-value
DLCO (% pred.)	–0.27	–0.30	–0.35 to –0.19	<0.001
Sex, female	0.07	<0.001	–3.57 to 3.72	0.968
Augmentation therapy	9.40	0.23	5.88 to 12.91	<0.001
Occupational dust exposure	6.04	0.15	2.43 to 9.65	0.001
Dependent variable: SGRQ total-score				

Abbreviations: CI, confidence intervals; DLCO, diffusion capacity; SGRQ, St George's Respiratory Questionnaire; % pred., % of the predicted normal value.

Table S5 Linear multivariate regression analysis: association between annual change in SGRQ total-score and exacerbation frequency adjusted for sex, age, augmentation therapy and occupational dust exposure

Variable	Unstandardized coefficient, B	Standardized coefficient, β	95% CI	*P*-value
Exacerbation frequency in follow-up period	0.68	0.15	0.15 to 1.20	0.011
Sex, female	−0.43	−0.05	−1.56 to 0.69	0.449
Age (years)	0.03	0.07	−0.02 to 0.08	0.233
Augmentation therapy	−1.21	−0.11	−2.59 to 0.16	0.082
Occupational dust exposure	0.12	0.01	−1.00 to 1.24	0.830
Dependent variable: ΔSGRQ total-score/year				

Abbreviations: CI, confidence intervals; SGRQ, St George's Respiratory Questionnaire.

2.3 Exacerbations and duration of smoking abstinence are associated with the annual loss of FEV_1 in individuals with PiZZ alpha-1-antitrypsin deficiency

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Exacerbations and duration of smoking abstinence are associated with the annual loss of FEV_1 in individuals with PiZZ alpha-1-antitrypsin deficiency

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ABSTRACT

Background: Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder that is associated with a higher risk of chronic obstructive pulmonary disease (COPD) and emphysema. The annual declines in lung function (FEV_1) and transfer factor of the lung for carbon monoxide (TLCO) predict all-cause mortality.
Material and methods: We investigated the longitudinal follow-up data over 11 years (mean follow-up period of 4.89 years) from the German AATD registry and analyzed the relationship between annual loss of FEV_1 and TLCO and sex, age, body mass index (BMI), nicotine consumption, occupational dust exposure, St. George's Respiratory Questionnaire (SGRQ) score, baseline FEV_1 or TLCO, alpha-1-antitrypsin (AAT) serum level, exacerbation frequency and the duration of smoking abstinence by multiple linear generalized estimating equations models (GEE-models).
Results: We evaluated the data of 100 individuals with post-bronchodilator FEV_1 measurements and from 116 individuals with TLCO measurements. The mean overall decline was -54.06 ± 164.62 ml/year in FEV_1 and -0.17 ± 0.70 mmol/min/kPa/year in TLCO. Accelerated deterioration of FEV_1 was associated with occupational dust exposure ($p = 0.026$), shorter duration of smoking abstinence ($p = 0.008$), higher baseline FEV_1 ($p = 0.003$), higher annual exacerbation frequency ($p = 0.003$) and higher frequency of glucocorticoids intake ($p = 0.004$).
Furthermore, patients with an elevated decline in TLCO showed significant impaired health-related quality of life at baseline ($p = 0.039$) and lower AAT serum levels ($p < 0.001$) in multivariate analysis.
Conclusions: Annual decline in FEV_1 is related to the exacerbation rate, occupational dust exposure and the duration of smoking abstinence.

1. Introduction

Alpha-1-antitrypsin -deficiency (AATD) is a genetic disorder that is associated with a reduced inhibition of neutrophil elastase and that leads to a higher risk of chronic obstructive pulmonary disease (COPD). The genotype PiZZ is clinically most relevant and is related to reduced lung functional parameters, reduced transfer factor of the lung for carbon monoxide (TLCO), lower alpha-1-antitrypsin (AAT) serum level and higher mortality [1–3].

Considering the longitudinal course of disease, several studies demonstrated the annual decrease in forced expiratory volume in 1 s (FEV_1) and TLCO as predictors for all-cause mortality [4–7].

The FEV_1 is subjected to physiological variation across the duration of a person's life. In childhood and adolescence, there is a rise in lung function, followed by a plateau phase with stable

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levels of lung function, followed by the start of lung function decline [8,9]. In addition to the lung function, the TLCO undergoes a physiological alteration across lifetime [10]. The decline in FEV_1 as well as the decline in TLCO depends on the initial baseline level: the lower the baseline FEV_1, the less the decline in the follow-up period [11,12].

Prior studies have showed that smoking cessation leads to a normalization of FEV_1 decline towards the values of never-smokers over time [13–15]. However, there is not much data about the effect of smoking cessation on the FEV_1 decline in individuals with AATD. Previous studies showed an association between faster decline in FEV_1 and lower body mass index (BMI), lower reversibility to bronchodilator (BDR), higher exacerbation rate and worse St. George's Respiratory Questionnaire (SGRQ) activity-score in individuals with AATD [11,12].

The aim of this paper was to analyze the change of FEV_1 and TLCO in individuals with AATD over a longer observation period and to identify factors that are associated with rapid decline.

We focused on the association between the duration of smoking abstinence and the decline in FEV_1 and TLCO. In addition, we analyzed the relationship between sex, age, BMI, occupational dust exposure, SGRQ score, baseline FEV_1 or TLCO, AAT serum level, the exacerbation frequency and the annual decline in FEV_1 (ΔFEV_1/yr) and TLCO (ΔTLCO/yr).

2. Material and methods

2.1. Structure of German registry for individuals with AATD

The German AATD registry (AATDR) was established in 2003 and is located at the Saarland University, Homburg. The registry is based on a rolling inclusion of individuals with severe AATD. The registry currently contains the data of 1086 patients (3/2016).

The dataset of AATDR is structured in a similar way to the dataset of the Alpha One International Registry (AIR).

The AATDR includes individuals with severe AAT deficiency, as defined by a known genotype or by low serum concentrations of AAT. Ethical approval for the questionnaires and the data storage concept were granted by the ethics committees of the Marburg University, the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (all in Germany). A declaration of informed consent was signed by all individuals.

2.2. Questionnaire design

The AATDR baseline questionnaire queries information about basic anthropomorphic data, AATD genotype, smoking habits, COPD exacerbation frequency within the last two years, pulmonary functional parameters, quality of life and pulmonary diseases, e.g. chronic bronchitis, emphysema or asthma bronchiale. The questionnaires are sent to affected individuals or their physicians. Questions on treatment, pulmonary function and the TLCO are answered by the treating physician.

Exacerbations are defined as an excessive worsening of COPD symptoms with a duration of more than two days that required hospitalization or treatment with antibiotics or systemic glucocorticoids. The definition of “exacerbation” was explained in the questionnaires to the participants. We obtained information of exacerbations within the last two years by baseline questionnaires and by follow-up questionnaires. Health-related quality of life data was collected with the SGRQ.

For the analysis of disease progression, we evaluated baseline data from 2004 and follow-up assessments from the years 2006, 2011 and 2015.

2.3. Data analysis

Data from 2004 to March 2016 were compiled and analyzed. At that time, 1086 patients were registered in the database including 876 individuals with PiZZ AATD. For the cross-sectional analysis, data on post-bronchodilator FEV_1 of 413 individuals and on TLCO of 484 individuals were available. Patients with lung transplantation or lung volume reduction in the follow-up period were excluded from the longitudinal study. The longitudinal study population contained 177 PiZZ AATD individuals with available follow-up data about ΔFEV_1/yr or/and about ΔTLCO/yr. We analyzed 100 individuals in the ΔFEV_1 analysis and 116 individuals in the ΔTLCO analysis. For our study, 95 individuals participated in the first follow-up survey (2006), 106 individuals in the second survey (2011) and 61 individuals in the third survey (2015). A number of participants were lost for the follow-up surveys. Reasons cannot be specified in detail (delivery failure of questionnaires due to movements, loss of interest by the participants or missing data about FEV_1 or TLCO, mortality, etc.). Fig. 1 shows the study enrollment process and the numbers of cases of valid data for the investigated variables.

2.4. Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD). The mean values of continuous variables in different groups were compared by independent samples *t*-test. The effects of the analyzed variables on the decline in FEV_1 or TLCO were evaluated by multiple linear generalized estimating equations models (GEE-models). The GEE approach was established by Liang and Zeger (1986) and Zeger and Liang (1986) for the evaluation of longitudinal data [16,17]. Using this model, we could assess multiple follow-up surveys of each individual. The influences of the variables were expressed in univariate analysis and verified by multivariate analysis. Taking into consideration that the baseline FEV_1 may influence the amount of decline in the follow-up period, this parameter was included in some of our multivariate regression models. To avoid multicollinearity in the multivariate analysis, we only included predictor variables which affected the deterioration of FEV_1 or TLCO independently of each other variable. Thus, not all potential confounders (e.g. age) could be considered. We specified the B value which indicates the change in deterioration of FEV_1 (ml/year) or TLCO (mmol/min/kPa/year) for a one-unit increase in the predictor variable. In the binomial predictor variables, B value indicates the difference in loss of FEV_1 (ml/year) or TLCO (mmol/min/kPa/year) between the two groups. Statistical significance was considered for two-sided p values less than 0.05. The analysis was performed using MS Excel and IBM SPSS version 23.

3. Results

3.1. Characteristics of patients

100 PiZZ AATD individuals (male n = 65; female n = 35) with available longitudinal post-bronchodilator FEV_1 data and 116 PiZZ AATD individuals (male n = 72; female n = 44) with available longitudinal TLCO data were analyzed (all together n = 177). 95 PiZZ individuals were available for the first follow-up survey in the year 2006, 106 PiZZ individuals for the second follow-up survey in the year 2011 and 61 PiZZ individuals for the third follow-up survey in the year 2015. The baseline characteristics are summarized in Table 1.

The mean age of the individuals for the longitudinal FEV_1 – and TLCO analysis (n = 177) was 55.2 ± 10.8 years (range: 31–78 years), mean BMI was 24.5 ± 4.4 kg/m^2. Ex-smokers (n = 125; 70.6%) had a

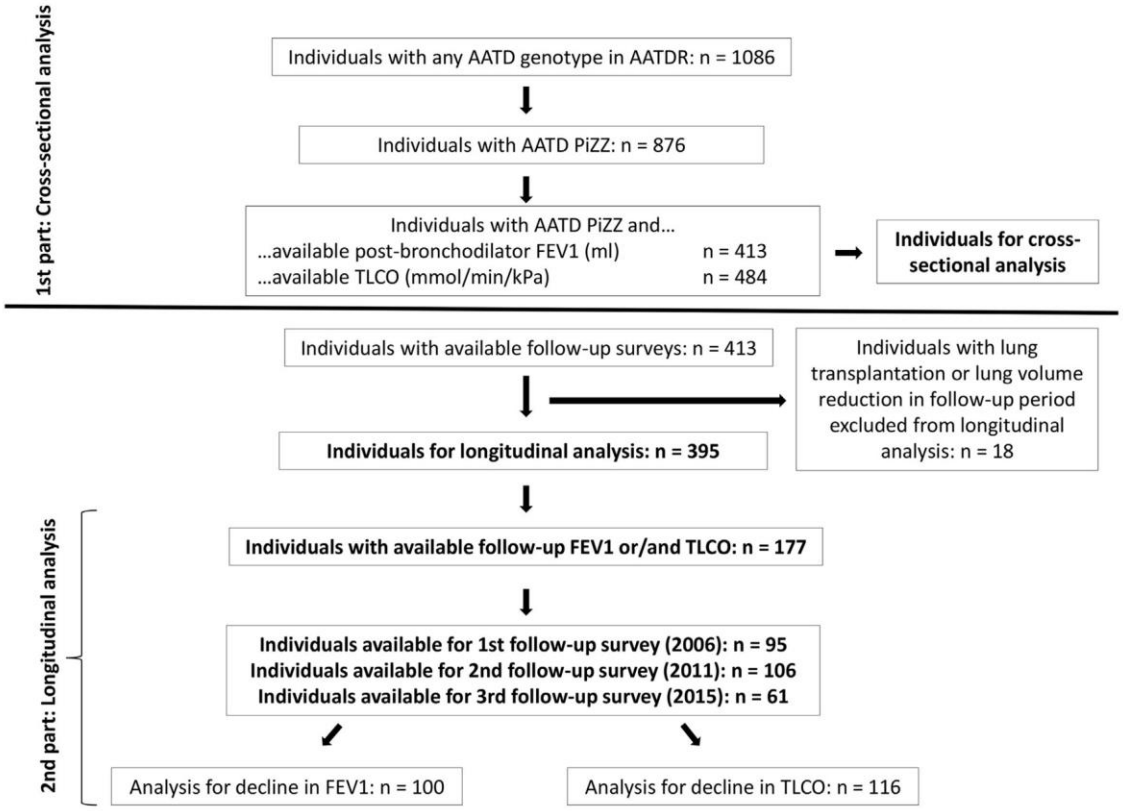

Fig. 1. Flow chart showing study enrollment process (n = 177).

Table 1
Baseline characteristics of individuals for longitudinal analysis.

	Individuals for longitudinal analysis (n = 395) Mean (SD)/n (%)	Individuals with available follow-up FEV_1 or/and TLCO (n = 177) Mean (SD)/n (%)	Individuals available for 1st follow-up survey (n = 95) Mean (SD)/n (%)	Individuals available for 2nd follow-up survey (n = 106) Mean (SD)/n (%)	Individuals available for 3rd follow-up survey (n = 61) Mean (SD)/n (%)
Sex (male)	239 (60.5%)	117 (66.1%)	61 (64.2%)	73 (68.9%)	40 (65.6%)
Age (years)	54.4 (11.6)	55.2 (10.8)	55.7 (10.3)	55.6 (11.0)	53.2 (9.9)
BMI (kg/m^2)	24.4 (4.6)	24.5 (4.4)	24.2 (3.5)	24.9 (4.8)	24.3 (3.6)
Never-smokers	104 (26.3%)	47 (26.6%)	21 (22.1%)	30 (28.3%)	15 (24.6%)
Ex-smokers	281 (71.1%)	125 (70.6%)	72 (75.8%)	73 (68.9%)	44 (72.1%)
Current smokers	9 (2.3%)	5 (2.8%)	2 (2.1%)	3 (2.8%)	2 (3.3%)
Packyears current smokers	25.8 (14.2)	29.2 (11.8)	34.7 (3.3)	31.2 (15.1)	31.4 (15.7)
Packyears ex-smokers	20.3 (14.3)	20.2 (14.0)	21.8 (15.5)	18.5 (12.2)	18.0 (13.2)
Baseline post-bronchodilator FEV_1 (ml)	1595 (674)	1671 (671)	1465 (532)	1759 (716)	1881 (717)
Baseline post-bronchodilator FEV_1 (% pred.)	48.9 (18.1)	51.0 (17.7)	46.4 (15.9)	53.2 (18.7)	55.9 (18.9)
Baseline TLCO (mmol/min/kPa)	4.97 (2.26)	5.06 (2.24)	4.94 (2.26)	5.29 (2.28)	4.96 (1.69)
Baseline TLCO (% pred.)	50.6 (20.2)	51.6 (20.8)	51.0 (21.6)	53.5 (21.1)	50.9 (16.3)

smoking history of 20.2 ± 14.0 packyears; current smokers (n = 5; 2.8%) of 29.2 ± 11.8 packyears. Mean baseline post-bronchodilator FEV_1 was 1671 ± 671 ml (% pred. 51.0 ± 17.7); mean baseline TLCO was 5.06 ± 2.24 mmol/min/kPa (% pred. 51.6 ± 20.8). We compared the individuals that were available for FEV_1 and/or TLCO follow-up assessments (n = 177) with the individuals that were lost during the follow-up period (n = 477). Individuals that were not available for follow-up surveys did not differ significantly from individuals with existing follow-up data in baseline FEV_1 (1526 ± 685 ml vs. 1664 ± 663 ml; p = 0.058), baseline TLCO (5.01 ± 2.54 mmol/min/kPa vs. 4.96 ± 2.29 mmol/min/kPa; p = 0.857), baseline SGRQ (46.89 ± 20.25 vs. 47.22 ± 17.60; p = 0.846) and the exacerbation frequency within the last two years (0.86 ± 1.07 vs. 0.77 ± 1.02; p = 0.339).

3.2. The cumulative nicotine consumption and exacerbation frequency are associated with worse baseline FEV_1 and TLCO in cross-sectional analysis

In the cross-sectional analysis, we evaluated data on all PiZZ individuals with at least one available FEV_1 (n = 413) and/or TLCO (n = 484) measurement (all together n = 654). The baseline FEV_1 (ml) correlated weakly but significantly with age (r = −0.172; p < 0.001), BMI (r = 0.121; p = 0.015), cumulative nicotine

consumption in packyears ($r = -0.147$; $p = 0.003$), the exacerbation frequency ($r = -0.286$; $p < 0.001$) and stronger with the SGRQ score ($r = -0.503$; $p < 0.001$). The baseline TLCO (mmol/min/kPa) was weakly but significantly associated with age ($r = -0.368$; $p < 0.001$), BMI ($r = 0.156$; $p = 0.001$), cumulative nicotine consumption in packyears ($r = -0.144$; $p = 0.002$), the exacerbation frequency ($r = -0.169$; $p < 0.001$) and SGRQ score ($r = -0.356$; $p < 0.001$). Neither the baseline FEV_1 nor the baseline TLCO were significantly dependent on the number of years since quitting smoking ($r = -0.030$; $p = 0.596$; $r = -0.036$; $p = 0.503$).

3.3. The highest decline of FEV_1 is observed in younger individuals (longitudinal analysis)

Analysis of decline is based on 177 PiZZ individuals with available follow-up data on FEV_1 and/or TLCO. The overall mean decline in FEV_1 was -54.06 ± 164.62 ml/year (Fig. 2). Younger individuals (aged 25–39 years) had the highest decline (-147.57 ± 163.59 ml/year), whereas older individuals (≥60 years) showed the lowest loss of lung function in the follow-up period (-34.80 ± 118.09 ml/year) ($p = 0.020$) (Table 2). Similar results were observed in the subgroup of never- and ex-smokers.

Mean overall decline in TLCO was -0.17 ± 0.70 mmol/min/kPa/year (Table 2; Fig. 3). The highest deterioration of TLCO was seen in older individuals (≥60 years) (-0.24 ± 0.89 mmol/min/kPa/year), the lowest decline in younger individuals (aged 25–39 years) (-0.09 ± 0.39 mmol/min/kPa/year) (the difference was not significant).

3.4. Accelerated deterioration of FEV_1 is associated with higher exacerbation frequency and shorter duration of smoking abstinence (longitudinal analysis)

Univariate analysis showed that the decline in FEV_1 was significantly associated with the annual exacerbation rate ($B = -79.110$; $p = 0.003$), the annual intake of glucocorticoids ($B = -78.353$; $p = 0.004$), occupational dust exposure ($B = -61.448$; $p = 0.026$), the duration of smoking abstinence in years ($B = 2.692$; $p = 0.008$) and baseline FEV_1 ($B = -0.050$; $p = 0.003$) (Table 3).

In consideration of several potential confounders, multivariate analysis confirmed the relationship between accelerated decline in FEV_1 and increased exacerbation frequency ($B = -44.877$; $p = 0.014$), the need of glucocorticoids ($B = -43.985$; $p = 0.020$) (both adjusted for sex, dust exposure, augmentation therapy, baseline FEV_1 and years of smoking abstinence) and a shorter duration of smoking abstinence in years ($B = 2.729$; $p = 0.011$)

Table 2
Mean annual decline stratified according to age groups, all individuals. The highest decline in FEV_1 is seen in younger individuals (25–39 years), the highest decline in TLCO is seen in older individuals (≥60 years).

	Mean ΔFEV_1 (ml/yr)	Mean ΔTLCO (mmol/min/kPa/yr)
Overall	−54.06 (164.62) (n = 100)	−0.17 (0.70) (n = 116)
25–39 yrs	−147.57 (163.59) (n = 9)	−0.09 (0.39) (n = 8)
40–59 yrs	−52.66 (191.38) (n = 51)	−0.13 (0.60) (n = 67)
≥ 60 yrs	−34.80 (118.09) (n = 40)	−0.24 (0.89) (n = 41)

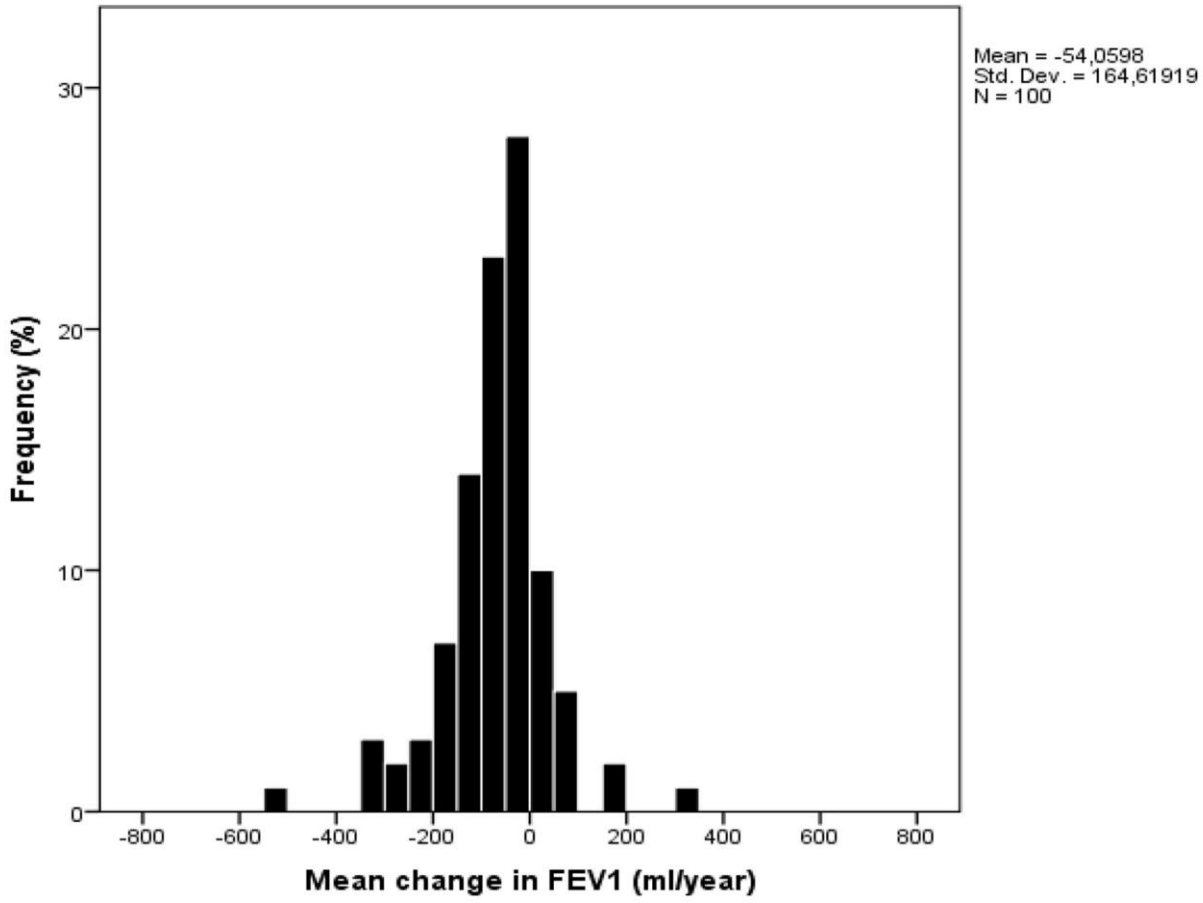

Fig. 2. The mean change in postbronchodilator FEV_1 was −54.06 ml in n = 100 individuals over the follow-up period (average of multiple follow-up surveys for each individual).

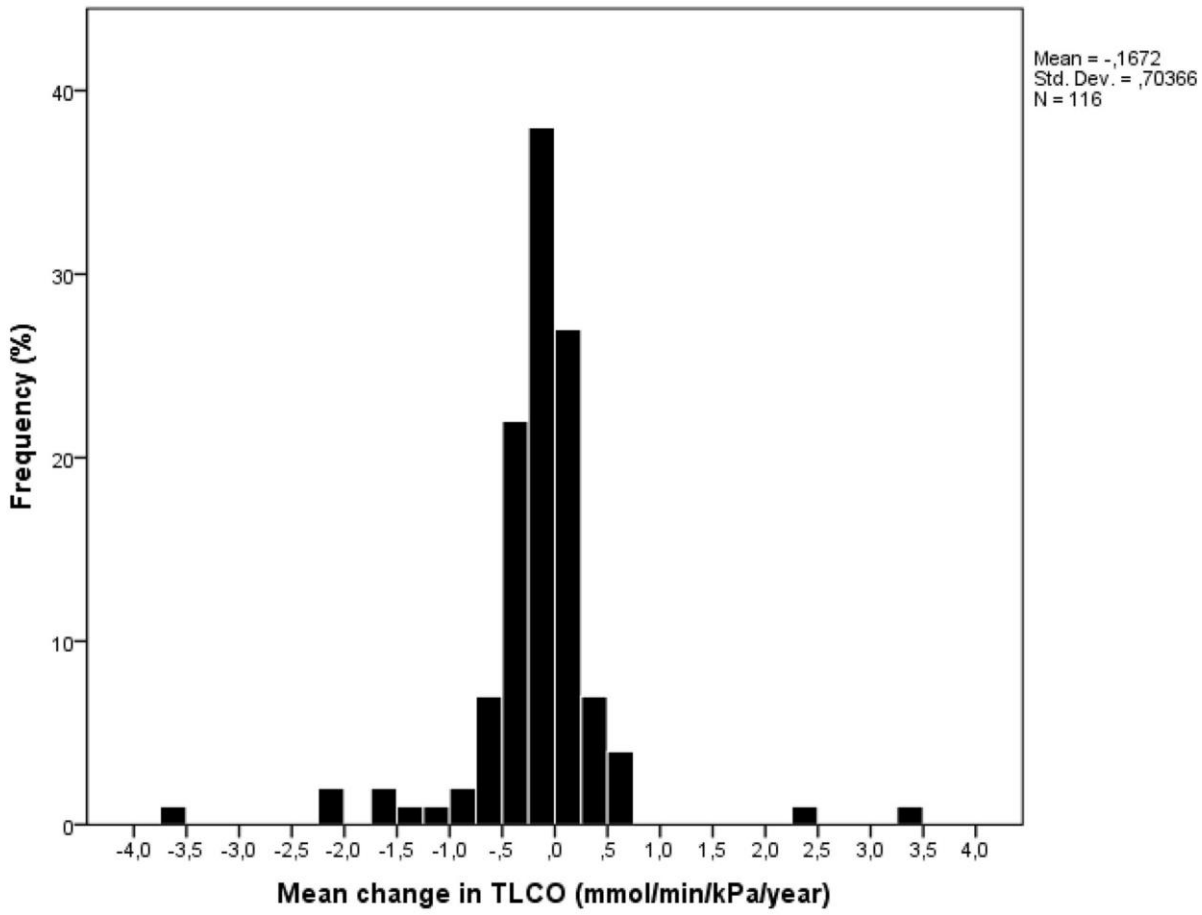

Fig. 3. The mean change in TLCO was −0.17 mmol/min/kPa/year in n = 116 individuals over the follow-up period (average of multiple follow-up surveys for each individual).

(adjusted for sex, dust exposure, augmentation therapy and baseline FEV_1). For example, the B value equal to −44.877 means that a one-unit increase in the annual exacerbation frequency is associated with a change in deterioration of FEV_1 of −44.877 ml/year.

3.5. Increased decline in TLCO is associated with lower baseline quality of life (SGRQ) (longitudinal analysis)

Univariate analysis revealed significant higher rates of decline in TLCO for low BMI (B = 0.023; p = 0.040) and higher SGRQ total-scores (B = −0.008; p = 0.027) at baseline. Multivariate analysis showed a significant relationship between deterioration of TLCO and baseline SGRQ total-score (B = −0.07; p = 0.039) (adjusted for baseline FEV_1, AAT serum level and chronic bronchitis), AAT serum level (B = 0.022; p < 0.001) (adjusted for baseline FEV_1 and chronic bronchitis) and baseline FEV_1 (B = 0.0003; p = 0.020) (adjusted for AAT serum level and chronic bronchitis) (Table 4).

The exacerbation frequency, the need of glucocorticoids or antibiotics or the rate of hospitalizations were not significantly associated with the loss of TLCO.

3.6. Comparison of augmented and not augmented individuals with AATD (longitudinal analysis)

In our study population, most of the subjects (n = 140; 79.1%) received augmentation therapy. A small sample size of 37 (20.9%) individuals reported no augmentation therapy. The differences in mean decline in FEV_1 (augmented: −48.96 ± 168.46 ml/yr (available in n = 85 individuals); not augmented: −82.94 ± 142.51 ml/yr (available in n = 15 individuals)) and TLCO (augmented: −0.15 ± 0.75 mmol/min/kPa/yr (available in n = 87 individuals); not augmented: −0.22 ± 0.53 mmol/min/kPa/yr (available in n = 29 individuals)) between individuals who reported on augmentation therapy and who did not were not significant.

4. Discussion

The main findings of the present study are significant relationships between the annual loss of FEV_1 and the exacerbation frequency and the duration of smoking abstinence. A higher exacerbation frequency and a short duration of smoking abstinence were associated with a faster deterioration of FEV_1. In our analysis, a GEE-model was chosen that enabled the interpretation of longitudinal registry data over 11 years (mean follow-up period of 4.89 years). Using this model, multiple observations for each subject could be assessed and several potential confounders could be included in the analysis.

In contrast to other AATD studies [11,12,18], we analyzed the impact of occupational dust exposure, the duration of smoking abstinence until the baseline lung function measurement after quitting smoking, the frequency of intake of glucocorticoids and antibiotics and the hospitalization rate.

In AATD, data on the age-dependent shape of decline in FEV_1 and TLCO and factors that accelerate the deterioration, is limited

Table 3
GEE-model analysis of variables influencing annual decline in FEV_1 (n = 100). B value indicates the change in deterioration of FEV_1 (ml/year) for a one-unit increase in the predictor variable. In binomial predictor variables, B value indicates the difference in loss of FEV_1 (ml/year) between the two groups. The exacerbation frequency, the glucocorticoids intake and the duration of smoking abstinence are significantly associated with the annual decline in FEV_1 in univariate and multivariate analysis (predictor variables in bold indicate significance in both univariate and multivariate analysis).

Predictor variable	Univariate analysis	Multivariate analysis
	B value (p value) n = 100	B value (p value) n = 100
Sex (male)	−32.704 (p = 0.217)	−44.392 (p = 0.029)
Age (years)	1.853 (p = 0.102)	1.320 (p = 0.267)
Cumulative nicotine consumption (packyears)	0.012 (p = 0.992)	0.060 (p = 0.965)
Chronic bronchitis	36.505 (p = 0.233)	2.504 (p = 0.902)
Emphysema	61.477 (p = 0.387)	26.681 (p = 0.660)
BMI (kg/m^2)	−0.017 (p = 0.992)	1.792 (p = 0.414)
Height (m)	−1.253 (p = 0.332)	−0.996 (p = 0.331)
Weight (kg)	−0.259 (p = 0.575)	0.431 (p = 0.467)
SGRQ total-score	0.198 (p = 0.730)	1.058 (p = 0.020)
AAT serum level (mg/dl)	0.403 (p = 0.591)	−0.051 (p = 0.939)
Exacerbation rate/yr	**−79.110 (p = 0.003)**	**−44.877 (p = 0.014)**
Glucocorticoids/yr	**−78.353 (p = 0.004)**	**−43.985 (p = 0.020)**
Increase of current medication/yr	−28.698 (p = 0.513)	−61.574 (p = 0.004)
Antibiotics/yr	−36.170 (p = 0.328)	−40.472 (p = 0.007)
Hospitalization/yr	18.424 (p = 0.846)	−22.268 (p = 0.479)
Occupational dust exposure	−61.448 (p = 0.026)	−17.104 (p = 0.388)
Duration of smoking abstinence (years)	**2.692 (p = 0.008)**	**2.729 (p = 0.011)**
Baseline FEV_1 (ml)	−0.050 (p = 0.003)	−0.018 (p = 0.306)
Baseline FEV_1 (% pred.)	−1.279 (p = 0.106)	−1.019 (p = 0.159)
Baseline TLCO (mmol/min/kPa)	−1.480 (p = 0.730)	1.174 (p = 0.749)
Baseline TLCO (% pred.)	0.591 (p = 0.323)	0.681 (p = 0.167)

[11,12]. For the analysis, all subjects were stratified into three age groups, because in the general population the decline in FEV_1 and TLCO varies depending on the subjects' age [10,19]. In our study, younger individuals (aged 25–39 years) showed a significant higher mean decline in FEV_1 compared to older subjects (≥60 years). We found no significant differences between the age groups for the decline in TLCO, however, there was a trend for an accelerated decline in older individuals. Viegi et al. found that the annual decline in TLCO is accelerated with higher age in healthy individuals (≥40 years old) [10]. Previous studies on healthy individuals showed a physiological annual change in FEV_1 of approximately −21 ml for non-/ex-smoking persons in middle age (40–59 years) [20]. We could show that middle-aged AATD patients (40–59 years) have an accelerated decline in FEV_1 that is more than 3-times higher compared to healthy persons. AATD subjects from the AATDR have a higher annual decline in FEV_1 (overall −54 ml/year) than individuals with non-AATD COPD from the ECLIPSE study cohort (−33 ml/year in 40–75 year-old ex- and current smokers) or the Lung Health Study (−27 ml/year in ex-smokers) [21,22]. These findings concur with the results from prior AATD studies that found an overall annual deterioration of FEV_1 of −54 ml/year, −50 ml/year, −67 ml/year and −57 ml/year [11,12,23,24].

The present paper investigated several factors that could

Table 4
GEE-model analysis of variables influencing annual decline in TLCO (n = 116). B value indicates the change in deterioration of TLCO (mmol/min/kPa/year) for a one-unit increase in the predictor variable. In binomial predictor variables, B value indicates the difference in loss of TLCO (mmol/min/kPa/year) between the two groups. The SGRQ score, the AAT serum level and the baseline FEV_1 are significantly associated with the annual decline in TLCO in multivariate analysis (predictor variables in bold indicate significance in both univariate and multivariate analysis).

Predictor variable	Univariate analysis	Multivariate analysis
	B value (p value) n = 116	B value (p value) n = 116
Sex (male)	−0.048 (p = 0.640)	−0.316 (p = 0.121)
Age (years)	−0.004 (p = 0.549)	−0.004 (p = 0.482)
Cumulative nicotine consumption (packyears)	0.005 (p = 0.168)	0.004 (p = 0.184)
Chronic bronchitis	−0.153 (p = 0.178)	−0.344 (p = 0.069)
Emphysema	0.279 (p = 0.205)	0.770 (p = 0.151)
BMI (kg/m^2)	0.023 (p = 0.040)	0.008 (p = 0.635)
Height (m)	−0.003 (p = 0.507)	−0.006 (p = 0.226)
Weight (kg)	0.003 (p = 0.386)	−0.001 (p = 0.788)
SGRQ total-score	**−0.008 (p = 0.027)**	**−0.07 (p = 0.039)**
AAT serum level (mg/dl)	0.016 (p = 0.054)	0.022 (p < 0.001)
Exacerbation rate/yr	−0.091 (p = 0.514)	−0.051 (p = 0.724)
Glucocorticoids/yr	−0.091 (p = 0.509)	−0.067 (p = 0.654)
Increase of current medication/yr	0.067 (p = 0.591)	0.079 (p = 0.529)
Antibiotics/yr	−0.101 (p = 0.295)	−0.068 (p = 0.463)
Hospitalization/yr	−0.433 (p = 0.080)	−0.446 (p = 0.098)
Occupational dust exposure	−0.054 (p = 0.662)	−0.214 (p = 0.278)
Duration of smoking abstinence (years)	−0.002 (p = 0.764)	0.003 (p = 0.714)
Baseline FEV_1 (ml)	0.0003 (p = 0.096)	0.0003 (p = 0.020)
Baseline FEV_1 (% pred.)	0.011 (p = 0.075)	0.012 (p = 0.005)
Baseline TLCO (mmol/min/kPa)	−0.019 (p = 0.371)	−0.014 (p = 0.577)
Baseline TLCO (% pred.)	−0.002 (p = 0.407)	−0.002 (p = 0.611)

influence the annual loss of FEV_1 and TLCO. Exacerbations have been identified as a risk factor for worse prognosis in non-AATD COPD [25]. Previous AATD studies showed a relationship between higher exacerbation rate and accelerated decline in FEV_1 [11,12]. Our results confirmed this relationship. In the follow-up, mean decline in FEV_1 was −116 ml/yr in individuals with frequent self-reported exacerbations (≥2/yr) compared to −21 ml/yr in individuals with no exacerbations. Moreover, frequent exacerbation-related glucocorticoids intake correlated with an accelerated decline in FEV_1, which underlines the role of moderate or severe exacerbations on the loss of lung function.

So far, the effect of smoking cessation on the deterioration of FEV_1 has not been investigated in individuals with AATD. It has been shown only in COPD subjects and in healthy individuals that sustained smoking abstinence leads to a return of the rate decline in FEV_1 to that of never-smokers [13–15]. To our knowledge, this is the first paper that revealed that a longer duration of smoking abstinence was associated with a lower decline in FEV_1 in individuals with AATD. This finding was confirmed by multivariate analysis under consideration of several confounders (sex, occupational dust exposure, augmentation therapy, duration of smoking abstinence and baseline FEV_1).

In contrast to the duration of smoking abstinence, the cumulative nicotine consumption in patients' prehistory was not significantly associated with a higher decline in FEV_1. This finding contributes to prior studies that showed a normalization of decline in FEV_1 after quitting smoking in COPD and healthy individuals [13–15]. A comparison between current smokers and ex-smokers in the deterioration of FEV_1 or TLCO was not possible because the number of current smoker in the registry was too small.

The annual decline in TLCO correlated significantly with the baseline SGRQ score. The worse the quality of life score at baseline, the stronger the decline in TLCO in the follow-up. These results underline the role of SGRQ as a good parameter for the estimation of disease progression.

Finally, we investigated the longitudinal follow-up data regarding the AAT augmentation therapy. There was a trend towards lower decline in FEV_1 and TLCO in augmented individuals, however, it was not significant. For a firm conclusion concerning augmentation therapy, the number of not augmented individuals in the registry was too small.

The main strengths of our study are the long follow-up period of 11 years (mean follow-up period of 4.89 years) and the large study group of the AATDR. However, only a part of the study group was available for the follow-up surveys and questionnaires were not filled out completely. This could be a reason for the missing significance in some predictors for the decline in FEV_1 or TLCO. Some more limitations to our study should be noted. First, the findings are based on self-reported information (e.g. exacerbations, lung function data); the quality of these data is likely less as compared to well-controlled clinical trials. Our data might not be representative for all individuals with AATD because individuals with more severe manifestations or increased burden of symptoms might be overrepresented. A part of the baseline study population was lost during the follow-up period. Nevertheless, the individuals that were not available for follow-up assessments did not have significantly worse FEV_1, TLCO and SGRQ at baseline and did not have significantly more exacerbations.

We conclude from our data that AATD individuals have a higher annual deterioration of FEV_1 than healthy subjects or non-AATD COPD individuals. Accelerated decline was associated with frequent exacerbations and glucocorticoids intake as well as a shorter period of smoking abstinence. The longer the period of smoking abstinence, the lower the annual loss of lung function.

List of abbreviations

AATD	Alpha-1-antitrypsin deficiency
COPD	Chronic obstructive pulmonary disease
PiZZ	Protease inhibitor ZZ genotype
TLCO	Transfer factor of the lung for carbon monoxide
AAT	Alpha-1-antitrypsin
FEV_1	Forced expiratory volume in 1 s
BMI	Body mass index
BDR	Airway obstruction: reversibility to bronchodilator/ bronchodilator response
SGRQ	St. George's Respiratory Questionnaire
ΔFEV_1/yr	Annual decline in FEV_1
ΔTLCO/yr	Annual decline in TLCO
AATDR	German alpha-1-antitrypsin deficiency registry
AIR	Alpha One International Registry
GEE-models	Generalized estimating equations models

Ethics approval and consent to participate

The questionnaires and the data storage concept were approved by the ethics committees of the Marburg University and the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (all in Germany). A declaration of informed consent was signed by all participating individuals.

Availability of data and materials

The datasets of the AATDR are located at the Department of Internal Medicine V – Pulmonology, Allergology, Intensive Care Medicine, Saarland University Hospital, Homburg, Germany and are available from the corresponding author on reasonable request.

Competing interests

RB, SF and CV have obtained research support and travel sponsoring from Talecris/Grifols and CSL Behring. CV has received honoraria for speaking engagements and for chairing a research prize committee from Talecris/Grifols. PL has received speaker fees from Talecris/Grifols. The authors alone are responsible for the content and the writing of the paper.

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Authors‘ contributions

All co-authors agreed to be accountable for all aspects of the work and reviewed the final manuscript. NB, PL, CV, RB, and SF contributed to conception of the study, patient recruitment and original data collection and interpretation. MS contributed to the patient recruitment. SW performed the statistical analysis.

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2.4 Intensive smoking diminishes the differences in quality of life and exacerbation frequency between the alpha-1-antitrypsin deficiency genotypes PiZZ and PiSZ

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Intensive smoking diminishes the differences in quality of life and exacerbation frequency between the alpha-1-antitrypsin deficiency genotypes PiZZ and PiSZ

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ABSTRACT

Background: Alpha-1-antitrypsin deficiency (AATD) is a rare genetic disorder that is associated with low levels of circulating alpha-1-antitrypsin in serum. In comparison to the genotype PiZZ, PiSZ usually leads to lower risk of emphysema, better lung function and better survival.
The aim of this study was to analyze the relationship between cigarette smoking (packyears) and the AATD genotypes (PiZZ and PiSZ) concerning quality of life (SGRQ), transfer factor of the lung for carbon monoxide (TLCO), forced expiratory volume in one second (FEV_1) and exacerbation rate.
Methods: We compared PiZZ and PiSZ individuals from the German registry for individuals with AATD (AATDR) in univariate analysis and multivariate linear regression models. All subjects were stratified into three groups according to their cumulative nicotine consumption (0 py; 0 < py < 30; ≥30 py).
Results: 868 PiZZ individuals (mean age 52.6 ± 12.8 years (43.5% female)) and 114 PiSZ individuals (mean age 50.3 ± 17.4 years (46.5% female)) were compared.
In contrast to never- and intensive (ex-) smokers, moderate (ex-) smoking PiSZ individuals had a significantly better SGRQ total score (B = −8.148; p = 0.020) and less exacerbations (B = −0.354; p = 0.037) than individuals with PiZZ in multivariate analysis.
Conclusions: The differences in quality of life and exacerbation frequency between PiZZ and PiSZ individuals diminish by intensive (ex-) smoking.

1. Introduction

Alpha-1-antitrypsin -deficiency (AATD) is a genetic disease that is caused by different genetic mutations which lead to lower circulating levels of alpha-1-antitrypsin (AAT) in serum. Because of the reduced inhibition of the neutrophil elastase and the aggregation of misfolded proteins in the hepatocytes, affected persons have an increased risk to develop chronic obstructive pulmonary disease (COPD) with emphysema and liver cirrhosis [1,2]. The protein is encoded by the SERPINA1 gene, of which about 100 genetic variants have been identified [3]. The most common deficiency alleles are the protease inhibitor Z (PiZ) and the protease inhibitor S (PiS) allele, that are named after their position on the gel after isoelectric focusing. The highest prevalence (1:1500–2000) of homozygous protease inhibitor ZZ genotype (PiZZ) AATD in Europe is found in the Baltic Republics or Denmark [4]. In Germany, the prevalence of PiZZ is estimated at about 1:10.300. The frequency of protease inhibitor SZ genotype (PiSZ) in Western Europe is even much higher, with an estimated prevalence of about 1:2400 in Germany [5]. However, the identification of individuals with PiSZ AATD in screening programs is lower in comparison to the identification of individuals with PiZZ AATD [6]. In most national AATD registries, PiSZ individuals are only a small part of the whole registry population [7–10].

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Previous studies suggest that the genotype PiSZ is associated with a milder reduction of AAT serum levels, a lower risk of emphysema, better lung function and a better survival in comparison to PiZZ [11–15].

Cigarette smoking is a predictor for the impairment in FEV_1 and TLCO in AATD PiZZ individuals [16]. In international AATD guidelines, there is a clear recommendation for early cessation of smoking particularly in individuals with the homozygous phenotype PiZZ [3]. Due to difficulties in the recruitment and identification of PiSZ subjects, only a few studies have analyzed the effects of smoking in PiSZ individuals in comparison to PiZZ individuals. Recent studies from the United Kingdom AATD registry revealed a reduced susceptibility to cigarette smoke for PiSZ individuals compared to PiZZ subjects concerning forced expiratory volume in one second (FEV_1), risk for chronic bronchitis and emphysema [13]. Piras et al. showed for any given quantity of smoking packyears, that the FEV_1 in PiSZ subjects was 20–30% better than in PiZZ subjects [15]. However, there is a lack of studies about the different vulnerabilities in PiSZ and PiZZ for the effects of smoking on the exacerbation frequency and quality of life.

In our study, we focused on the exacerbation rate and the St. George's Respiratory Questionnaire (SGRQ) score in addition to the FEV_1 and the transfer factor of the lung for carbon monoxide (TLCO). Both, frequency of severe exacerbations and SGRQ were demonstrated as prognostic relevant parameters in non-AATD COPD [17–19].

The aim of the study was to investigate the differences of FEV_1, TLCO, SGRQ and the exacerbation frequency between PiZZ and PiSZ individuals in context to the smoking history.

2. Materials and methods

2.1. The German registry for individuals with AATD

The German registry for individuals with AATD (AATDR) is a questionnaire-based collection of data (1079 individuals (01/2016)). It was established in 2003 and is continuously enrolling individuals with AATD [8]. The AATDR consists of two parts, one part for adult individuals and another part for AATD individuals under 18 years. Most of included subjects were invited to participate by direct mailing involving physicians and patient groups. The AATDR provides its data to the Alpha One International Registry (AIR), which bundles the information of 21 national registries [20].

Subjects who fulfilled the inclusion criteria of severe AAT deficiency, expressed by known genotypes were asked for their contact information for further follow-up surveys. These personal data are stored separately from the subjects' clinical information. The questionnaires and the data storage concept were approved by the ethics committees of the Marburg University, the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (Germany). Individuals registered in the database filled an informed consent.

2.2. Structure of questionnaire

The AATDR collects the information by a 10-page questionnaire that was sent to affected individuals and their physicians. The participants were asked to inform about their liver diseases and pulmonary diseases, e.g. liver cirrhosis, elevated liver enzymes, chronic bronchitis, emphysema or pneumonia. The subjects reported the number of COPD exacerbations within the last two years. Exacerbations were defined as an excessive worsening of COPD symptoms with a duration of more than two days that required hospitalization or treatment with antibiotics or systemic glucocorticoids. To calculate the cumulative nicotine consumption in packyears all subjects were asked to inform about their smoking history. The affected individuals fill in most of the questions. However, several items of the questionnaire had to be completed by the physician, e.g. questions on treatment and pulmonary function. Health-related quality of life was collected in a second part of the survey with the SGRQ. The fulfilled questionnaires were archived in a MS Access 2010 −database.

2.3. Data analysis

Until January of 2016, 1076 individuals were registered in our database, among them 868 individuals with PiZZ and 114 individuals with PiSZ alpha-1-antitrypsin-deficiency. The subjects' data were collected and transferred into MS Excel and SPSS. Fig. 1 shows the study enrollment process and the numbers of cases of valid data.

To assess the impact of inhalative exposure to cigarette smoke on the investigated parameters, all subjects were stratified in different groups according to their smoking history in packyears (0 py/never-smokers; 0 < py < 30; ≥30 py). There is no single, generally accepted threshold (packyears) for intensive smoking. According to the study by Badgett et al. in individuals with non-AATD-COPD, obstructive lung disease could be identified with a sensitivity of 98 percent if subjects smoked more than 30 packyears [21]. Therefore, the threshold for intensive (ex-) smoking was defined for ≥ 30 packyears in the present study.

The date of inclusion of the individuals in the registry varied by months to years due to the enrolling recruitment strategy.

2.4. Statistical analysis

Categorical data are displayed by absolute and relative frequencies (percentages). The comparison of qualitative variables was performed by Chi-squared test and by Fisher's test if the expected frequencies were lower than 5. Continuous variables were expressed as means ± standard deviation (SD). The mean values of continuous variables in different groups were compared by independent samples *t*-test. In addition, multivariate linear regression analysis considered the individuals' age as a potential confounder. Because of collinearity between age and packyears, not both variables were taken into the regression model. Statistical significance was taken at two-sided p values less than 0.05. The analysis was performed by IBM SPSS version 23.

3. Results

3.1. Characteristics of individuals

The data of 868 PiZZ AATD subjects (female n = 378) and 114

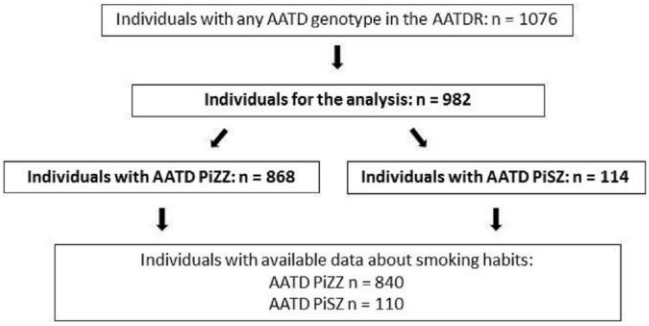

Fig. 1. Flow chart showing study enrollment process.

Table 1
Baseline characteristics.

Variable			
	PiZZ n = 868	**PiSZ n = 114**	
	Mean (SD)/n (%)	**Mean (SD)/n (%)**	p value
Age (years)	52.6 (12.8)	50.3 (17.4)	0.185
Sex (male)	490 (56.5%)	61 (53.5%)	0.552
BMI (kg/m^2)	24.34 (4.62)	24.31 (5.49)	0.945
AAT serum concentration (mg/dl)	28.13 (13.52)	58.12 (16.27)	*< 0.001*
Nicotine consumption:			
Never-smokers	222 (25.6%)	33 (28.9%)	0.444
Ex-smokers	617 (71.1%)	65 (57.0%)	*< 0.001*
Current smokers	24 (2.8%)	16 (14.0%)	
Packyears	15.75 (16.42)	20.38 (22.24)	0.037
Age diagnosis (years)	47.4 (14.1)	47.6 (18.3)	0.906
Delay of diagnosis (years)	8.17 (10.40)	9.60 (10.45)	0.242
Reason of diagnosis:			
Pulmonary disease	688 (79.3%)	81 (71.1%)	*0.001*
Liver disease	29 (3.3%)	2 (1.8%)	
Other disease	24 (2.8%)	3 (2.6%)	
Family screening	69 (7.9%)	23 (20.2%)	
Population screening	2 (0.2%)	0 (0.0%)	
Other reason	40 (4.6%)	2 (1.8%)	
Clinical presentation:			
Pulmonary disease	775 (89.3%)	84 (73.7%)	*< 0.001*
Chronic bronchitis	403 (46.4%)	51 (44.7%)	0.858
Emphysema	713 (82.1%)	60 (52.6%)	*< 0.001*
Asthma bronchiale	147 (16.9%)	22 (19.3%)	0.475
Bronchiectasis	45 (5.2%)	2 (1.8%)	0.156
Others	56 (6.5%)	12 (10.6%)	0.122
Previous pneumonia	418 (48.2%)	40 (35.1%)	*0.009*
Times of pneumonia	0.98 (1.99)	0.56 (1.09)	*0.001*

PiSZ subjects (female n = 53) were analyzed. Mean age of PiZZ individuals was 52.6 ± 12.8 years and 50.3 ± 17.4 of PiSZ individuals. Mean body mass index (BMI) was nearly the same in PiZZ and PiSZ.

The cohort of included PiZZ individuals had a significant lower AAT serum concentration at diagnosis compared to PiSZ individuals (PiZZ: 28.1 ± 13.5 mg/dl; PiSZ: 58.1 ± 16.3 mg/dl; $p < 0.001$). Ex-smokers had a smoking history of 23.5 ± 13.2 packyears (py) in PiZZ and of 29.9 ± 21.1 packyears in PiSZ; current smokers (PiZZ 2.8%; PiSZ 14%) of 26.7 ± 9.9 and 26.2 ± 22.2 packyears. The cumulative nicotine consumption in packyears was significantly higher in PiSZ subjects ($p = 0.037$). There was no difference in the age of diagnosis between the genotypes PiZZ and PiSZ. The delay between the first symptoms and the establishment of the correct diagnosis was longer in PiSZ, but not significant ($p = 0.242$). The most common reason for diagnosis was "pulmonary disorder" in both genotypes, followed by "family screening". PiZZ individuals reported significantly more "pulmonary disease" ($p < 0.001$). In addition, individuals with PiZZ reported significantly more often "emphysema" ($p < 0.001$) and "pneumonias" ($p = 0.009$). The baseline characteristics are summarized in Table 1.

3.2. Differences between PiZZ and PiSZ in SGRQ, TLCO and the exacerbation rate diminish with rising packyears (univariate analysis)

Individuals with available data about the smoking habits (n = 840 PiZZ; n = 110 PiSZ) were divided into three groups according to their smoking history in cumulative packyears (0 py/never-smokers; 0 < py < 30; ≥30 py).

The univariate analysis (Table 2) showed the following results:

In the group of never-smokers, PiZZ subjects had significantly worse TLCO ($p = 0.003$), SGRQ total score ($p = 0.002$), symptoms score ($p = 0.049$), activity score ($p < 0.001$) and impacts score ($p = 0.005$). The difference between PiZZ and PiSZ in FEV_1 was

Table 2
PiZZ and PiSZ individuals stratified according to the cumulative nicotine consumption. Independent samples t-test showed significant differences between PiZZ and PiSZ only in never-smokers and moderate (ex-) smokers, but not in intensive (ex-) smokers.

Variable	**PiZZ** Mean (SD) age: 52.7 (12.8) yrs. Sex: 43.4% female	**PiSZ** Mean (SD) age: 50.1 (17.5) yrs. Sex: 47.3% female	p value
	Never-smokers (0 py) Mean (SD) age: 53.7 (18.5) yrs. Sex: 52.7% female		
	n = 223 Mean (SD) age: 55.5 (17.3) yrs. Sex: 53.4% female	n = 33 Mean (SD) age: 41.3 (22.0) yrs. Sex: 48.5% female	
Exacerbation rate within the last 2 years	0.59 (0.97)	0.66 (0.94)	0.723
FEV_1 (l)	1.74 (0.80)	2.43 (1.01)	0.050
FEV_1 (% pred.)	61.6 (21.0)	74.4 (27.2)	0.199
TLCO (mmol/min/kPa)	5.77 (3.12)	8.11 (3.27)	*0.003*
TLCO (% pred.)	61.9 (27.6)	81.1 (26.0)	*0.005*
SGRQ total score	36.85 (21.80)	22.48 (21.60)	*0.002*
SGRQ symptoms score	44.52 (23.76)	35.01 (23.86)	*0.049*
SGRQ activity score	45.28 (26.78)	25.16 (29.59)	*<0.001*
SGRQ impacts score	28.66 (21.48)	16.66 (19.28)	*0.005*
	Moderate (ex-) smokers (0 < py < 30) Mean (SD) age: 51.6 (11.6) yrs. Sex: 41.9% female		
	n = 491 Mean (SD) age: 51.7 (11.2) yrs. Sex: 41.3% female	n = 44 Mean (SD) age: 50.5 (15.8) yrs. Sex: 47.7% female	
Exacerbation rate within the last 2 years	0.87 (1.08)	0.51 (0.91)	*0.019*
FEV_1 (l)	1.57 (0.68)	1.87 (1.16)	0.297
FEV1 (% pred.)	46.9 (18.6)	56.5 (26.3)	0.156
TLCO (mmol/min/kPa)	4.89 (2.24)	5.75 (3.42)	0.278
TLCO (% pred.)	49.1 (19.9)	61.9 (34.9)	0.121
SGRQ total score	46.88 (19.77)	38.88 (25.55)	0.083
SGRQ symptoms score	55.67 (22.66)	43.32 (28.24)	*0.009*
SGRQ activity score	58.30 (22.63)	48.82 (30.35)	0.070
SGRQ impacts score	37.28 (21.04)	28.98 (24.34)	*0.023*
	Intensive (ex-) smokers (≥ 30 py) Mean (SD) age: 52.8 (8.7) yrs. Sex: 35.8% female		
	n = 126 Mean (SD) age: 51.3 (8.0) yrs. Sex: 33.3% female	n = 33 Mean (SD) age: 58.2 (9.0) Sex: 45.4% female	
Exacerbation rate within the last 2 years	1.02 (0.99)	0.90 (1.05)	0.537
FEV_1 (l)	1.46 (0.55)	1.59 (1.00)	0.647
FEV1 (% pred.)	42.8 (14.8)	44.7 (20.3)	0.687
TLCO (mmol/min/kPa)	4.51 (1.76)	4.55 (4.24)	0.972
TLCO (% pred.)	44.8 (15.8)	51.6 (39.4)	0.507
SGRQ total score	53.22 (16.54)	59.84 (19.01)	0.069
SGRQ symptoms score	62.84 (19.73)	62.12 (20.70)	0.857
SGRQ activity score	67.46 (18.12)	71.59 (20.10)	0.273
SGRQ impacts score	41.87 (18.74)	49.22 (22.30)	0.065

borderline significant ($p = 0.050$). No significant differences were observed for the exacerbation frequency ($p = 0.723$).

In PiZZ and PiSZ subjects with moderate nicotine consumption ($0 < py < 30$) significance could be noted for the exacerbation rate within the last two years ($p = 0.019$). The SGRQ total score was higher (worse) in subjects with PiZZ, however not significant ($p = 0.083$). Significant differences between PiZZ and PiSZ for SGRQ scores were only found in the symptoms score ($p = 0.009$) and the impacts score ($p = 0.023$).

Individuals with PiSZ, who smoked 30 packyears or even more had no significant lower exacerbation frequency in comparison to PiZZ individuals ($p = 0.537$). The SGRQ, TLCO and thelung function did not differ significantly between the genotypes. Figs. 2–5 illustrate the differences between PiZZ and PiSZ in the packyears groups.

3.3. The association between the genotype PiSZ and better SGRQ and lower exacerbation frequency is only significant in moderate (ex-) smokers (multivariate linear regression analysis)

Multivariate linear regression analysis was calculated for each dependent variable (Table 3). The association between the AATD genotype (PiZZ/PiSZ) and the dependent variable was controlled for the subjects' age. In addition to the two-tailed significance, we specified the unstandardized coefficient B. The B value expresses the adjusted difference of PiSZ to PiZZ individuals in the dependent variable.

In the group of never-smokers as well as in the group of intensive (ex-) smokers, the genotype was not significantly associated with the exacerbation frequency, the FEV_1 and TLCO or the SGRQ scores. There was a significant association between the genotype PiSZ and better SGRQ total score ($B = -8.148$; $p = 0.020$)

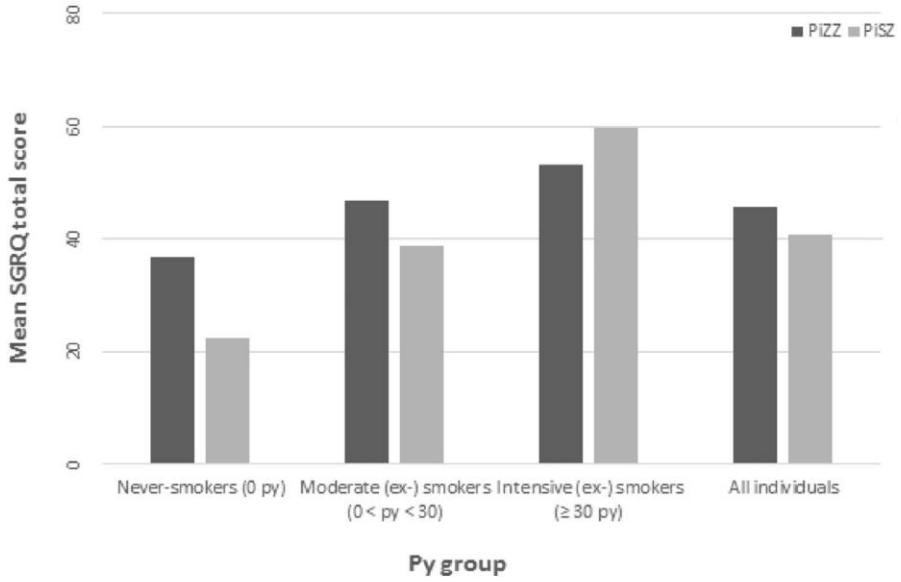

Fig. 2. Differences in SGRQ total score between PiZZ and PiSZ by smoking groups and globally (univariate analysis). Significant differences between the genotypes were found in never-smokers (p = 0.002). Globally, there were no significant differences.

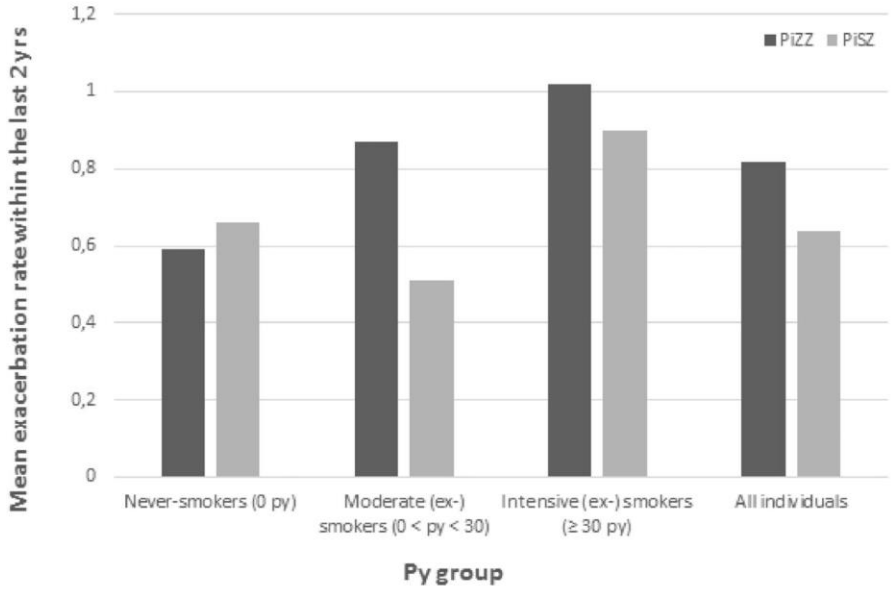

Fig. 3. Differences in the exacerbation frequency within the last two years between PiZZ and PiSZ by smoking groups and globally (univariate analysis). Significant differences between the genotypes were found in moderate (ex-) smokers. There were no significant differences in never-smokers and intensive (ex-) smokers and globally.

(and all sub-scores) and a lower exacerbation frequency (B = −0.354; p = 0.037) in the group of moderate (ex-) smokers (0 < py < 30). In moderate (ex-) smokers, we found no significant relationship between the genotype and the FEV_1 (B = 0.314; p = 0.079) or the TLCO (B = 0.969; p = 0.057).

4. Discussion

The present study investigated the association between the different AATD genotypes PiZZ and PiSZ and smoking (packyears) in several clinical outcome parameters. The main finding of this study is that PiSZ individuals have less exacerbations and better SGRQ in comparison to PiZZ individuals in the group of moderate (ex-) smokers. These differences between the genotypes diminish in the group of intensive (ex-) smokers. Although the estimated prevalence of PiSZ in Germany is much higher compared to PiZZ [5], PiSZ individuals represent only a minority in the AATDR due to a lack of identification for the registry in the clinical routine. PiSZ subjects have a significant higher cumulative nicotine consumption in comparison to individuals with PiZZ.

Recent studies from the United Kingdom AATD registry revealed a difference in survival between the genotypes PiSZ and PiZZ in AATD and a lower susceptibility to cigarette smoke for PiSZ individuals regarding FEV_1, chronic bronchitis and emphysema [13].

Quality of life scores and the exacerbation frequency are widely used and well proven predictors for disease prognosis in non-AATD COPD [17–19]. The assessment of the exacerbation rate over a fixed period by questionnaires is a validated tool used in large prior

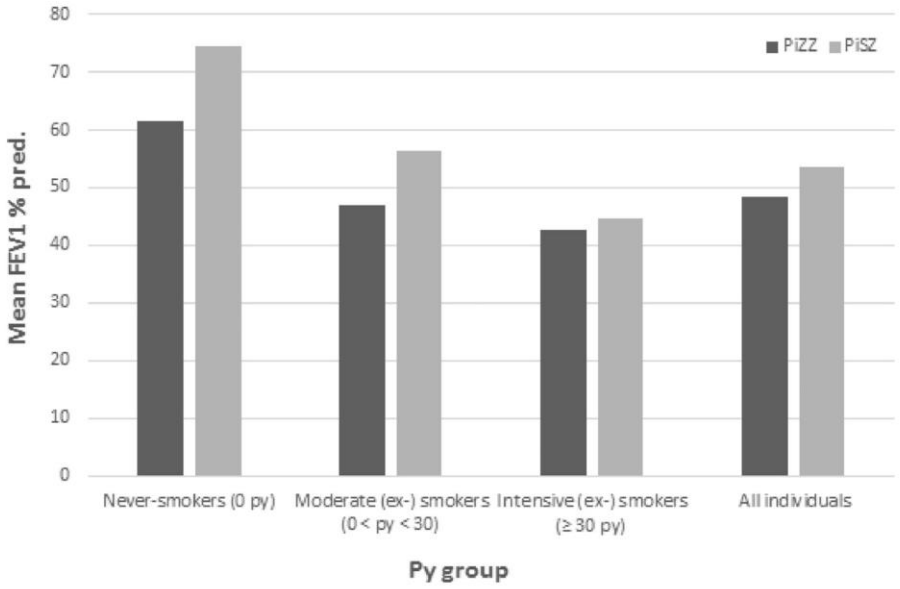

Fig. 4. Differences in FEV1% pred. between PiZZ and PiSZ by smoking groups and globally (univariate analysis). There were no significant differences between the genotypes.

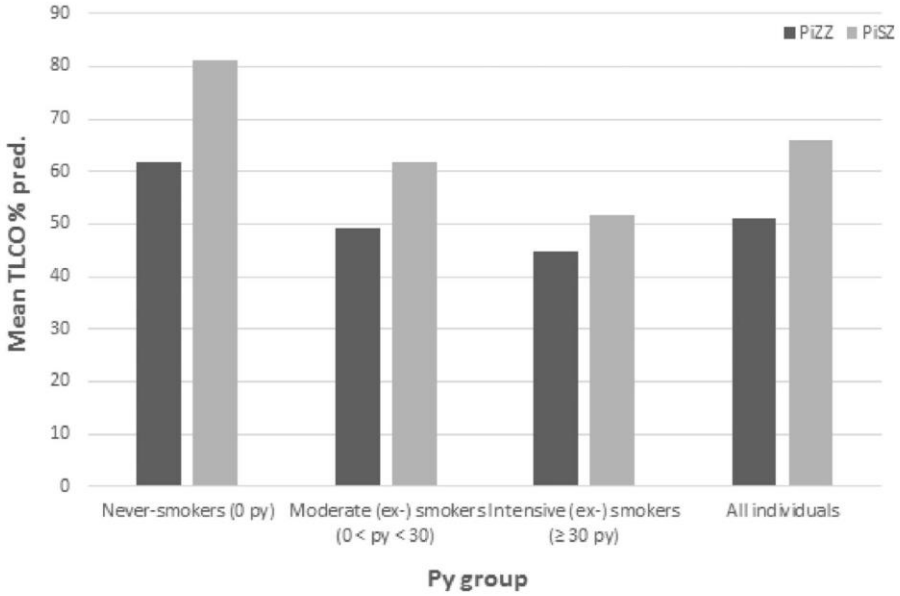

Fig. 5. Differences in TLCO % pred. between PiZZ and PiSZ by smoking groups and globally (univariate analysis). Significant differences between the genotypes were found in never-smokers ($p = 0.005$) and globally ($p = 0.003$).

studies such as the COPDGene study [22]. Until now, there is a lack of data about the different vulnerability to cigarette smoke for the exacerbation frequency and quality of life in PiZZ and PiSZ genotypes. Therefore, we focused on the exacerbation rate and SGRQ scores in context to the cumulative nicotine smoking. We evaluated the data of the AATDR in univariate analysis and in multivariate linear regression models. The study population was divided into three groups according to their smoking history in cumulative packyears (0 py/never-smokers; 0 < py < 30; ≥30 py). We chose the threshold for intensive (ex-) smoking at ≥ 30 packyears, because Badgett et al. showed, that obstructive lung disease could be identified with a sensitivity of 98 percent if subjects with non-AATD-COPD smoked more than 30 packyears [21].

In univariate analysis, significant differences between PiZZ and PiSZ were found in the group of never-smokers and in the group of moderate (ex-) smokers but not in intensive (ex-) smokers. However, in univariate analysis the subjects' age as a potential confounder was not considered. Therefore, we performed multivariate linear regression analysis including the genotype and the age. Due to collinearity between age and packyears not both variables were taken in the regression model. That is the reason for the categorization of all subjects in three packyears-groups in the multivariate models.

In multivariate analysis, we found no significant association between the genotype and exacerbations, quality of life, FEV_1 or TLCO in never-smoking AATD individuals. These results comply with the findings from Tanash et al. who described that the SGRQ total score does not differ between the genotypes PiZZ and PiSZ in

Table 3
Multivariate linear regression analysis: the association between the AATD genotype (PiZZ/PiSZ) and dependent variables adjusted for age (stratified according to the cumulative nicotine consumption into three groups). In addition to the two-tailed significance (*p value for the genotype as independent variable in the linear regression model), we specified the unstandardized coefficient B, the estimated effect of respective regression coefficients (β) and the 95% confidence interval. The B value expresses the differences of the genotype PiSZ to the genotype PiZZ. Significant better quality of life and lower exacerbation frequency for PiSZ individuals were found in the group of moderate (ex-) smokers (0 < py < 30).

Dependent variable	Unstandardized coefficient B	Standardized coefficient β	95% CI	p value*
Never-smokers (n = 223 PiZZ and 33 PiSZ individuals)				
Exacerbation rate within the last 2 years	0.227	0.080	−0.133 to 0.587	0.216
FEV_1 (l)	−0.117	−0.037	−0.760 to 0.526	0.718
TLCO (mmol/min/kPa)	0.657	0.070	−0.615 to 1.929	0.309
SGRQ total score	−4.297	−0.064	−11.899 to 3.306	0.266
SGRQ symptoms score	−2.106	−0.029	−10.822 to 6.609	0.634
SGRQ activity score	−5.962	−0.070	−14.702 to 2.778	0.180
SGRQ impacts score	−3.853	−0.060	−11.344 to 3.637	0.312
Moderate (ex-) smokers (0 < py < 30) (n = 491 PiZZ and 44 PiSZ individuals)				
Exacerbation rate within the last 2 years	−0.354	−0.092	−0.687 to −0.021	0.037
FEV_1 (l)	0.314	0.107	−0.037 to 0.665	0.079
TLCO (mmol/min/kPa)	0.969	0.104	−0.029 to 1.967	0.057
SGRQ total score	−8.148	−0.103	−15.033 to −1.263	0.020
SGRQ symptoms score	−12.178	−0.142	−19.519 to −4.836	0.001
SGRQ activity score	−9.143	−0.101	−16.647 to −1.639	0.017
SGRQ impacts score	−8.515	−0.103	−15.547 to −1.483	0.018
Intensive (ex-) smokers (≥ 30 py) (n = 126 PiZZ and 33 PiSZ individuals)				
Exacerbation rate within the last 2 years	−0.254	−0.100	−0.683 to 0.175	0.244
FEV_1 (l)	0.231	0.130	−0.140 to 0.603	0.219
TLCO (mmol/min/kPa)	0.595	0.096	−0.726 to 1.916	0.373
SGRQ total score	2.374	0.054	−4.947 to 9.695	0.523
SGRQ symptoms score	−2.753	−0.056	−11.126 to 5.620	0.517
SGRQ activity score	0.054	0.001	−7.567 to 7.674	0.989
SGRQ impacts score	2.720	0.055	−5.223 to 10.663	0.500

never-smoking AATD individuals [23]. In contrast, airflow obstruction was found to be less frequently among never-smoking PiSZ individuals compared to never-smoking PiZZ individuals [24].

Moderate (ex-) smoking PiSZ subjects had a significant lower exacerbation frequency and better SGRQ symptoms and impacts scores compared to PiZZ subjects in univariate analysis. In multivariate analysis, we confirmed a significant association between the genotype PiSZ and a lower exacerbation frequency and better quality of life. However, there was no significant relationship between the genotype and FEV_1 or TLCO in this smoking group. Results from earlier studies on individuals with non-AATD COPD showed that the FEV_1 alone does not reflect the heterogeneity of disease severity [25,26].

With increasing number of packyears (≥30 py) the significant differences in quality of life and exacerbation frequency were weakening and significance disappeared between the genotypes in univariate and multivariate analysis. We conclude that the increased susceptibility to smoking of PiZZ individuals compared to PiSZ individuals diminishes at high doses of smoking.

In the present study, PiSZ individuals had a significant higher cumulative nicotine consumption in comparison to PiZZ individuals. This concurs with the results from the Spanish AATD registry [10]. An explanation could be missing awareness in physicians and affected persons of the importance of smoking cessation for PiSZ subjects, due to the supposed milder form of disease. A further explanation might be the longer delay between the first symptoms and the establishment of the correct diagnosis in PiSZ subjects (not significant in this study) in consideration that most of the individuals quit smoking when obtaining the diagnosis of AATD.

The estimated prevalence of PiSZ AATD is much higher compared to PiZZ AATD [5]. Nevertheless, PiSZ individuals only represent a small part in the AATDR. Greulich et al. showed before us that the detection of PiSZ subjects in screening programs is much smaller than the identification of PiZZ subjects [6]. This might be due to a lack of awareness for testing COPD patients with milder symptoms. It is to be expected that undiagnosed PiSZ subjects are not advised to quit smoking in a same way as PiSZ individuals with a confirmed diagnosis.

Some limitations of this study must be taken into account based on the design of the registry. In the AATDR, individuals with more severe manifestations or higher burden of symptoms of the disease might be overrepresented. Therefore, the findings might not be representative for all subjects with AATD. Our results depend largely on self-reported information and the cooperation of the treating physician (e.g. lung function, exacerbations), so that the quality of data is likely less as compared to well-controlled clinical trials.

In conclusion, moderate (ex-) smoking individuals with PiSZ have less exacerbations and better quality of life in comparison to individuals with PiZZ. Intensive (ex-) smokers did not show significant differences between the genotypes PiZZ and PiSZ with regard to exacerbations and quality of life.

List of abbreviations

AATD	Alpha-1-antitrypsin deficiency
AAT	Alpha-1-antitrypsin
COPD	Chronic obstructive pulmonary disease
PiZ	Protease inhibitor Z allele
PiS	Protease inhibitor S allele
PiZZ	Protease inhibitor ZZ genotype
PiSZ	Protease inhibitor SZ genotype
FEV_1	Forced expiratory volume in one second
SGRQ	St. George's Respiratory Questionnaire
TLCO	Transfer factor of the lung for carbon monoxide
AATDR	German alpha-1-antitrypsin deficiency registry
AIR	Alpha One International Registry

SD Standard deviation
BMI Body mass index
Py Packyears
FEV_1% pred. FEV_1% of the predicted normal value
TLCO % pred. TLCO % of the predicted normal value

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Availability of data and materials

The data sets of the AATDR are located at the Department of Internal Medicine V – Pulmonology, Allergology, Intensive Care Medicine, Saarland University Hospital, Homburg, Germany and are available from the corresponding author on reasonable request.

Author contributions

NB, PML, CV, RB, and SF contributed to conception of the study, patient recruitment and original data collection and interpretation. MS contributed to the patient recruitment. SW supported the statistical analysis. The authors alone are responsible for the content and the writing of the paper. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Conflict of interests

RB, SF and CV have obtained research support and travel sponsoring from Talecris/Grifols and CSL Behring. CV has received honoraria for speaking engagements and for chairing a research prize committee from Talecris/Grifols. PML has received speaker fees from Talecris/Grifols. The authors report no other conflicts of interest in this work.

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3 Anhang

3.1 Register - Fragebögen

Deutsches Register für Patienten
mit Alpha-1-Antitrypsin-Mangel

Eingangsuntersuchung

α-1-ANTITRYPSIN
REGISTER

Registernummer
(bitte nicht ausfüllen)

Das Ausfüllen des Fragebogens dauert ungefähr 20 Minuten. Bitte versuchen Sie, die Fragen so genau wie möglich zu beantworten.

Einige Fragen können nur mit Hilfe Ihres Arztes beantwortet werden. Diese Fragen sind mit einem Ausrufezeichen markiert. Falls Sie die Fragen zur Lungenfunktion nicht beantworten können, bitten wir Sie, dass Sie sich von Ihrem Arzt eine Kopie der aktuellen und wenn möglich, auch der ersten bei Ihnen durchgeführten Lungenfunktion geben lassen. Diese senden Sie bitte mit dem Fragebogen an uns zurück.

Bei Fragen können Sie uns gerne kontaktieren:

Prof. Dr. med. Dr. rer. nat. Robert Bals
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Pneumologie, Allergologie, Beatmungs- und Umweltmedizin Gebäude 91
Kirrberger Straße
66421 Homburg/Saar

Allgemeine Angaben

Heutiges Datum _____

Geburtsjahr _____

Geburtsort _____

Geschlecht ☐ weiblich ☐ männlich

Körpergröße _____ cm

Gewicht _____ kg

Rauchgewohnheiten

Haben Sie irgendwann geraucht? ☐ Ja ☐ Nein

Falls JA, mit welchem Alter haben Sie mit dem Rauchen begonnen? _____ Jahre

Wie viele **Zigaretten** haben Sie am Tag geraucht / rauchen Sie derzeit? _____ Stück

Wie viele **Zigarren** haben Sie am Tag geraucht / rauchen Sie derzeit? _____ Stück

Wie viel Gramm Tabak rauchen Sie pro Woche? _____ g

Haben Sie mit dem Rauchen aufgehört? ☐ Ja ☐ Nein

Falls JA, mit welchem Alter haben Sie mit dem Rauchen aufgehört? _____ Jahre

Lebererkrankungen

Besteht bei Ihnen eine Leberzirrhose? ☐ Ja ☐ Nein

Falls JA, wann wurde diese diagnostiziert? _____

Bestand kurz nach Ihrer Geburt eine Gelbsucht (Ikterus)? ☐ Ja ☐ Nein

Wurde bei Ihnen ein Leberkrebs diagnostiziert? ☐ Ja ☐ Nein

Falls JA, wann wurde die Diagnose gestellt? _____

Wurde bei Ihnen eine Lebertransplantation durchgeführt? ☐ Ja ☐Nein

Falls JA, wann wurde die Transplantation durchgeführt? _____

Welche Lungenerkrankungen bestehen bei Ihnen?

Chronische Bronchitis	☐	Emphysem	☐
Asthma bronchiale	☐	Bronchiektasen	☐

Bestehen bei Ihnen weitere Lungenerkrankungen? ☐ Ja ☐ Nein

Falls JA, welche: _____

Mit welchem Alter begannen die Atembeschwerden? _____ Jahre

Was waren die wichtigsten Beschwerden zu Beginn? (Bitte nur 1 ankreuzen!)

Husten ohne Auswurf	☐
Husten mit Auswurf	☐
Atemnot in Ruhe	☐
Atemnot bei Belastung	☐
Anfallsweise Atemnot	☐

Wurde bei Ihnen ein Lungenkrebs diagnostiziert? ☐ Ja ☐ Nein

Falls JA, wann wurde die Diagnose gestellt? Datum: _____

Welcher Typ liegt vor ☐ kleinzellig ☐ nicht-kleinzellig

Fragen zu weiteren Erkrankungen

Leiden Sie an anderen Krankheiten außer der bisher genannten? ☐ Ja ☐ Nein

Falls JA, an welchen:

Diagnose 1 _____

Diagnose 2 _____

Diagnose 3 _____

Wurde bei Ihnen eine **Lungentransplantation** durchgeführt? ☐ Ja ☐ Nein

Falls JA, wann wurde die Transplantation durchgeführt? _____

Wurde bei Ihnen eine operative **Lungen-Volumenreduktion** durchgeführt? ☐ Ja ☐ Nein

Falls JA, wann wurde die Operation durchgeführt? _____

Hatten Sie jemals eine **Lungenentzündung** (Pneumonie)? ☐ Ja ☐ Nein

Falls JA, bitte angeben wie häufig: ____ mal, Häufigkeit nicht bekannt? ☐

Stehen Sie auf einer **Lungentransplantations-Warteliste**? ☐ Ja ☐ Nein

Falls Ja, seit welchem Datum? _____

Wurde ein Computertomogramm (CT) des Brustkorbs durchgeführt?

☐ Ja ☐ Nein ☐ Unbekannt

Falls JA, bitte Datum angeben: _____

Fragen zu Verschlechterungen des Krankheitsverlaufes, so genannten Exazerbationen

Eine Exazerbation ist eine Episode, in der sich die Symptomatik der Lungenerkrankung über das normale Maß hinaus verschlechtert. Die Dauer beträgt mehr als zwei Tage. Es ist eine Änderung der Therapie notwendig.

Hatten Sie solche Episoden während der letzten beiden Jahre? ☐ Ja ☐ Nein

Falls JA, wie oft? ☐ 1-2x, ☐ 2-4x, ☐ mehr als 4 x

Musste wegen einer der Episoden die Behandlung verändert werden? ☐ Ja ☐ Nein

Falls JA, ...	0x	1-2x	2-4x	mehr als 4 x
Wie oft war Cortison notwendig?	☐	☐	☐	☐
Wie oft war eine Steigerung der Medikamente notwendig?	☐	☐	☐	☐
Wie oft waren Antibiotika notwendig?	☐	☐	☐	☐
Wie oft mussten Sie stationär ins Krankenhaus?	☐	☐	☐	☐

Wie lange dauerte es bis Sie Ihren normalen Gesundheitszustand wieder erreichten? _____Tage

Fragen zur Berufstätigkeit

Üben Sie eine Berufstätigkeit aus? ☐ Ja ☐ Nein

Falls NEIN, bitte den Grund dafür angeben:

- Alter ☐
- Lebererkrankung ☐
- Lungenerkrankung ☐
- Andere ☐

Welchen Beruf üben Sie aus/haben Sie früher ausgeübt? _____

Sind/waren Sie während Ihrer Berufstätigkeit überdurchschnittlich stark Stäuben ausgesetzt? ☐ Ja ☐ Nein

Warum wurde bei Ihnen eine Alpha-1-Antitrypsin-Diagnostik durchgeführt?

Lungenerkrankung ☐
Lebererkrankung ☐
Andere Erkrankung ☐
Familienuntersuchung ☐
Bevölkerungsuntersuchung ☐
Anderer Grund ☐

Bitte fragen Sie hier Ihren Arzt.

Welcher Genotyp oder Phänotyp wurde festgestellt?

ZZ ☐
SZ ☐
Anderer ☐ Welcher ? _____

Wann wurde bei Ihnen ein Alpha-1-Antitrypsin-Mangel diagnostiziert? Datum: _____

Welcher Spiegel (Konzentration) an Alpha-1-Antitrypsin im Blut wurde (ohne Substitution) bei Ihnen gemessen? (Bitte die Einheit mit angeben, z.B. mg/dl, g/l oder µM) _____

Haben Sie Verwandte mit Alpha-1-Antitrypsin-Mangel? Ja ☐ Nein ☐ Nicht bekannt ☐

Fragen zur derzeitigen Therapie

Führen Sie derzeit eine Therapie zur **Erweiterung der Atemwege** durch (Sprays, Theophyllin)?

☐ Ja ☐ Nein ☐ Unbekannt

Führen Sie derzeit eine **Sauerstofflangzeit-Therapie** durch?

☐ Ja ☐ Nein ☐ Unbekannt

Erhielten Sie jemals eine **Substitutionsbehandlung mit Alpha-1-Antitrypsin**?

☐ Ja ☐ Nein

Falls JA, Beginn der Behandlung: _____

Dosierung der Behandlung: _____ g alle _____ Tage

Wurde die Behandlung wieder beendet? ☐ Ja ☐ Nein

Falls JA, wann wurde die Behandlung beendet? _____

Warum wurde die Behandlung beendet? _____

Aktuelle Lungenfunktion

Datum der aktuellen Lungenfunktion _____

Bitte fragen Sie hier Ihren Arzt.

Bitte legen Sie uns hier auch eine Kopie Ihres Lungenfunktion-Befundes bei.

	vor Broncholyse	nach Broncholyse
FEV1	_____ l	_____ l
FVC	_____ l	_____ l
VC	_____ l	_____ l

Wurde die Diffusionskapazität (TLCO) gemessen? ☐ Ja ☐ Nein

Datum der Messung _____

Messmethode ☐ Single breath ☐ Steady state

Einheit ☐ mmol/min/kPa ☐ ml/min/mmHg

Ergebnis _____

Welche Bezeichnung hat der Befund? ☐ TLCO ☐ TLCOc/ TLCO(Hb) ☐ Unbekannt/ andere

Frühere Lungenfunktion (am besten die älteste Lungenfunktion)

Datum der früheren Lungenfunktion _____

	vor Broncholyse	nach Broncholyse
FEV1	_____ l	_____ l
FVC	_____ l	_____ l
VC	_____ l	_____ l

Fragen zu Laboruntersuchungen

Wurden Leberenzyme bestimmt? ☐ Ja ☐ Nein

Falls JA, Datum der Bestimmung _____

Erhöhte ALAT/SGPT	☐ Ja	☐ Nein	☐ Keine Daten	☐ Nicht gemacht
Erhöhte ASAT/SGOT	☐ Ja	☐ Nein	☐ Keine Daten	☐ Nicht gemacht
Erhöhte GGT	☐ Ja	☐ Nein	☐ Keine Daten	☐ Nicht gemacht
Erhöhte ALP/AP	☐ Ja	☐ Nein	☐ Keine Daten	☐ Nicht gemacht

Fragen zur Lebensqualität

Mit diesem Fragebogen möchten wir mehr darüber erfahren, welche Beschwerden Ihnen Ihre Atmung bereitet und wie diese sich auf Ihr Leben auswirken. Wir möchten dadurch herausfinden, was Ihnen an Ihrer Erkrankung aus Ihrer Sicht die meisten Probleme bereitet, und nicht, was die Ärzte und das Pflegepersonal dazu meinen. Lesen Sie bitte die Anleitung sorgfältig durch und fragen Sie nach, wenn Sie etwas nicht verstehen. Denken Sie nicht zu lange über Ihre Antworten nach.

Bevor Sie den restlichen Fragebogen ausfüllen: Bitte kreuzen Sie die Beschreibung an, die nach Ihrer Beurteilung Ihrem jetzigen Gesundheitszustand entspricht:

Sehr gut	Gut	Mäßig	Schlecht	Sehr schlecht
☐	☐	☐	☐	☐

TEIL 1: *Diese Fragen beziehen sich auf die Häufigkeit Ihrer Atemwegsbeschwerden in den vergangenen 3 – 12 Monaten. Bitte kreuzen Sie für jede Frage 1 Kästchen an.*

	An den meisten Tagen der Woche	An mehreren Tagen der Woche	An ein paar Tagen im Monat	Nur bei Infektionen der Atemwege	Gar nicht
1. Während *des letzten Jahres* habe ich gehustet:	☐	☐	☐	☐	☐
2. Während *des letzten Jahres* habe ich Schleim (Auswurf) ausgehustet:	☐	☐	☐	☐	☐
3. Während *des letzten Jahres* war ich kurzatmig:	☐	☐	☐	☐	☐
4. Während *des letzten Jahres* hatte ich Anfälle von Keuchen oder Pfeifen beim Atemholen (Atemgeräusch):	☐	☐	☐	☐	☐

	Mehr als 3 Anfälle	3 Anfälle	2 Anfälle	1 Anfall	Keine Anfälle
5. Wie viele schwere oder sehr unangenehme Anfälle von Atemwegsbeschwerden hatten Sie in *dem vergangenen Jahr*:	☐	☐	☐	☐	☐

	1 Woche oder länger	3 Tage oder länger	1 oder 2 Tage	Weniger als 1 Tag
6. Wie lange dauerte der schlimmste Anfall von Atemwegsbeschwerden? (Wenn Sie keine schweren Anfälle hatten, gehen Sie von hier bitte direkt zu Frage 7).	☐	☐	☐	☐

	Kein Tag war gut	1 oder 2 gute Tage	3 oder 4 gute Tage	Fast jeder Tag war gut	Jeder Tag war gut
7. Wie viele gute Tage (d.h. Tage mit wenig Atemwegsbeschwerden) hatten Sie in einer durchschnittlichen *Woche in dem vergangenen Jahr?*	☐	☐	☐	☐	☐

	Nein	Ja
8. Wenn Sie pfeifend atmen oder keuchen, ist es morgens schlimmer?	☐	☐

TEIL 2

Abschnitt 1 *Wie würden Sie Ihr Atemleiden beschreiben? Bitte nur ein Kästchen ankreuzen:*

- ☐ Das wichtigste Problem, das ich habe
- ☐ Bereitet mir ziemlich viele Probleme
- ☐ Bereitet mir ein paar Probleme
- ☐ Bereitet mir keine Probleme

Wenn Sie berufstätig sind oder waren, kreuzen Sie bitte eines der Kästchen an:

- ☐ Ich habe wegen meiner Atemwegsbeschwerden ganz aufgehört zu arbeiten.
- ☐ Meine Atemwegsbeschwerden beeinträchtigen mich bei der Arbeit oder haben mich veranlasst, meinen Beruf / meine Stelle zu wechseln.
- ☐ Meine Atemwegsbeschwerden wirken sich nicht auf meine Arbeit aus.

Abschnitt 2 *Diese Fragen beziehen sich darauf, bei welchen Tätigkeiten Sie derzeit für gewöhnlich in Atemnot geraten. Bitte geben Sie in jeder Zeile an, was auf Sie zutrifft, indem Sie richtig oder falsch ankreuzen:*

	Richtig	Falsch
Still sitzen oder ruhig liegen	☐	☐
Sich waschen oder anziehen	☐	☐
Im Haus herumgehen	☐	☐
Draußen auf ebenen Wegen gehen	☐	☐
Einen Treppenabsatz hinaufgehen	☐	☐
Bergauf gehen	☐	☐
Sport treiben	☐	☐

Abschnitt 3 *Nun folgen weitere Fragen zu Ihrem derzeitigen Husten und Ihrer derzeitigen Kurzatmigkeit.*
Bitte geben Sie in jeder Zeile an, was auf Sie zutrifft, indem Sie richtig oder falsch ankreuzen:

	Richtig	Falsch
Mein Husten tut weh.	☐	☐
Mein Husten macht mich müde.	☐	☐
Ich gerate außer Atem, wenn ich rede.	☐	☐
Ich gerate außer Atem, wenn ich mich vornüber beuge.	☐	☐
Mein Husten oder mein Atem stören meinen Schlaf.	☐	☐
Ich bin schnell erschöpft.	☐	☐

Abschnitt 4 *Bei diesen Fragen geht es um weitere Auswirkungen, die Ihre Atemwegsbeschwerden derzeit möglicherweise auf Sie haben. Bitte geben Sie in jeder Zeile an, was auf Sie zutrifft, indem Sie richtig oder falsch ankreuzen:*

	Richtig	Falsch
Mein Husten oder mein Atmen ist mir in der Öffentlichkeit peinlich.	☐	☐
Meine Atemwegsbeschwerden sind lästig für meine Familie, meine Freunde oder Nachbarn.	☐	☐
Wenn ich keine Luft kriege, bekomme ich Angst oder gerate in Panik.	☐	☐
Ich habe das Gefühl, meine Atemwegsbeschwerden nicht im Griff zu haben.	☐	☐
Ich rechne nicht damit, dass es mit meinen Atemwegsbeschwerden besser wird.	☐	☐
Durch meine Atemprobleme bin ich anfällig oder invalide geworden.	☐	☐
Es ist für mich riskant, mich sportlich zu betätigen.	☐	☐
Alles erscheint mir mühsam.	☐	☐

Abschnitt 5 *Diese Fragen betreffen Ihre Medikamente. Wenn Sie keine Medikamente nehmen, gehen Sie bitte gleich zu Abschnitt 6 weiter.*
Bitte geben Sie in jeder Zeile an, was auf Sie zutrifft, indem Sie richtig oder falsch ankreuzen:

	Richtig	Falsch
Meine Medikamente helfen mir nicht viel.	☐	☐
Es ist mir peinlich, meine Medikamente in der Öffentlichkeit zu benutzen.	☐	☐
Meine Medikamente verursachen mir unangenehme Nebenwirkungen.	☐	☐
Meine Medikamente beeinträchtigen mein Leben erheblich.	☐	☐

Abschnitt 6 *Bei diesen Fragen geht es darum, wie sich Ihr Atemleiden möglicherweise auf Ihre Aktivität auswirkt. Bitte kreuzen Sie bei jedem Satz richtig an, wenn darin ein oder mehrere Fragestellungen aufgrund Ihres Atemleidens auf Sie zutreffen.*
Sonst kreuzen Sie bitte falsch an:

	Richtig	Falsch
Ich brauche lange, um mich zu waschen oder anzuziehen.	☐	☐
Ich kann kein Bad bzw. keine Dusche nehmen, oder ich brauche lange dazu.	☐	☐
Ich gehe langsamer als andere oder ich halte an, um mich auszuruhen.	☐	☐
Aufgaben wie Hausarbeit dauern sehr lange oder ich muss mich zwischendurch ausruhen.	☐	☐
Wenn ich einen Treppenabsatz hinaufgehe, muss ich langsam gehen oder zwischendurch anhalten.	☐	☐
Wenn ich mich beeile oder schnell gehe, muss ich danach anhalten oder langsamer gehen.	☐	☐

	Richtig	Falsch
Wegen meines Atemleidens fällt es mir schwer bergauf zu gehen, etwas die Treppen hoch zu tragen, leichte Gartenarbeit zu verrichten wie Unkraut jäten, zu tanzen, Bowling oder Golf zu spielen.	☐	☐
Wegen meines Atemleidens fällt es mir schwer, schwere Lasten zu tragen, den Garten umzugraben oder Schnee zu schippen, zu joggen oder schnell zu gehen (8 km/Stunde), Tennis zu spielen oder zu schwimmen.	☐	☐
Wegen meines Atemleidens fällt es mir schwer sehr schwere körperliche Arbeit zu verrichten, zu laufen, Rad zu fahren, schnell zu schwimmen oder anstrengenden Sport zu treiben.	☐	☐

Abschnitt 7 *Wir wüssten gerne, wie Ihre Atemwegsbeschwerden normalerweise Ihr tägliches Leben beeinflussen. Bitte kreuzen Sie bei jeder Frage richtig oder falsch an (bitte denken Sie daran, dass „richtig" nur auf Sie zutrifft, wenn Sie etwas aufgrund Ihrer Atemwegsbeschwerden nicht tun können):*

	Richtig	Falsch
Ich kann keinen Sport treiben	☐	☐
Ich kann nicht ausgehen, um mich zu unterhalten oder zu erholen	☐	☐
Ich kann das Haus nicht verlassen, um einkaufen zu gehen	☐	☐
Ich kann keine Hausarbeit verrichten	☐	☐
Ich kann mich nicht weit von meinem Bett oder meinem Stuhl entfernen	☐	☐

Es folgt eine Liste von weiteren Tätigkeiten, die Sie wegen Ihrer Atemwegsbeschwerden möglicherweise nicht ausüben können. (Sie brauchen diese nicht anzukreuzen. Die Liste soll Ihnen nur helfen, sich daran zu erinnern, wie Ihre Kurzatmigkeit Sie möglicherweise einschränkt).

- Spazierengehen oder den Hund spazieren führen
- Etwas im Haus oder im Garten erledigen
- Geschlechtsverkehr
- In die Kirche gehen oder an einen Ort, an dem Unterhaltung geboten wird
- Bei schlechtem Wetter nach draußen gehen oder verrauchte Räume betreten
- Familie oder Freunde besuchen oder mit Kindern spielen

Bitte notieren Sie, welchen anderen wichtigen Tätigkeiten Sie möglicherweise wegen Ihrer Atemwegsbeschwerden nicht nachgehen können:

_____

_____

_____

Wir möchten Sie nun bitten, die Feststellung (nur eine) anzukreuzen, die am besten beschreibt, wie sich Ihre Atemwegsbeschwerden auf Sie auswirken:

☐ Sie hindern mich nicht daran, das zu tun, was ich gerne möchte
☐ Sie hindern mich an ein oder zwei Dingen, die ich gerne tun möchte
☐ Sie hindern mich an den meisten Dingen, die ich gerne tun möchte
☐ Sie hindern mich an allem, was ich gerne tun möchte

Dies ist das Ende des Fragebogens. Vielen Dank für Ihre Mithilfe!

3.2 Fachzeitschriften-Artikel

3.2.1 Deutsche Medizinische Wochenschrift: Alpha-1-Antitrypsinmangel – was gibt es Neues?

Bernhard N, Bals R, Fahndrich S. [Alpha-1-antitrypsin deficiency - an update]. Dtsch Med Wochenschr. 2016;141(20):1467-9.

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Alpha-1-Antitrypsinmangel – was gibt es Neues?

Nikolas Bernhard, Robert Bals, Sebastian Fähndrich

Was ist neu?

- **Alpha-1-Antitrypsin-Testung:** Die Erkrankung ist immer noch stark unterdiagnostiziert – trotz einfacher, kostengünstiger Diagnostik. Insbesondere das Lungenunterlappen-betonte Emphysem sollte an einen Alpha-1-Antitrypsinmangel denken lassen.
- **CT-Densitometrie zur AAT-Substitutionstherapie:** Die Daten der RAPID-Studie konnten eine Verlangsamung der Krankheitsprogression im Sinne eines geringeren Lungendichteverlustes durch eine Alpha-1-Antitrypsin-Substitution zeigen. Die CT-Densitometrie ist der Verlaufsbeobachtung der Einsekunden und Diffusionskapazität überlegen. Je höher der therapeutische Alpha-1-Antitrypsin-Spiegel, desto geringer ist der Verlust an Lungendichte. Die Daten sprechen für eine möglichst frühe Einleitung einer Substitutionstherapie.

AAT-Testung

Der Alpha-1-Antitrypsinmangel (AATM) zählt zu den genetischen Ursachen für die Entwicklung einer chronisch obstruktiven Lungenerkrankung (COPD). Die durch den Mangel an AAT ausgelöste fehlende Neutralisierung proteolytischer Enzyme, insbesondere der neutrophilen Elastase, bewirkt eine chronische Inflammation und Destruktion des Lungengewebes. Gegenstand der aktuellen Forschung sind auch die immunmodulatorischen Eigenschaften des AAT-Proteins [1].

In Deutschland beträgt die Prävalenz für den mit teilweise schweren Krankheitsverläufen einhergehenden Phänotyp PiZZ etwa 1:10300 [2]. Erkenntnisse über die Erkrankung basieren zu einem erheblichen Anteil auf Daten nationaler Register.

Trotz zunehmendem Bewusstsein im klinischen Alltag und kostengünstiger etablierter Diagnostik, ist die Erkrankung immer noch stark unterdiagnostiziert. Bei COPD-Patienten und Patienten mit Lungenemphysem, die jünger als 45 Jahre sind oder keinen Risikofaktoren ausgesetzt waren, sollte auf das Vorliegen eines Alpha-1-Antitrypsinmangels getestet werden. Weiterhin ist eine Testung gemäß der Leitlinien [2] der American Thoracic Society (ATS) und European Respiratory Society (ERS) indiziert bei:

- Emphysem (v.a. Lungenunterlappen-betont) und COPD
- Asthma bronchiale mit nicht vollständiger Reversibilität der Atemwegsobstruktion,
- Bronchiektasen unklarer Genese,
- Neugeborenen, Kindern und Erwachsenen mit unklarer Lebererkrankung,
- asymptomatischen Patienten mit persistierender obstruktiver Lungenfunktionsstörung und positiver Raucheranamnese oder beruflicher Staubexposition,
- Erwachsenen mit nekrotisierender Pannikulitis sowie
- Blutsverwandten 1. Grades von AATM-Patienten.

Wichtig ist, dass die Testung im Infekt-freien Intervall durchgeführt wird, da AAT als Akute-Phase-Protein bei einem Infekt falsch negative Testergebnisse liefern kann. Der diagnostische Ablauf ist in ▶ **Abb. 1** dargestellt.

Der AAT-Spiegel kann in jedem Standard-Labor kostengünstig bestimmt werden. Des Weiteren besteht auch die Möglichkeit, das Blut auf einem Filterpapier zur kostenfreien Untersuchung an das Labor an der Klinik für Innere Medizin mit Schwerpunkt Pneumologie am Universitätsklinikum Marburg einzuschicken.

Therapeutisch steht die Entwöhnung inhalativen Zigarettenkonsums im Vordergrund. Auch wenn durch den AATM bereits zerstörtes Lungengewebe (Lungenemphysem) nicht restituierbar ist, steht die Aufhaltung der Krankheitsprogression im Vordergrund: Mit der rechtzeitigen Einhaltung einer Nikotinabstinenz, Prävention vor beruflicher Staubexposition und konsequenter Infektprophylaxe sollte das Fortschreiten der Erkrankung verzögert werden. Weiterhin kann der Krankheitsverlauf durch die intravenöse Substitution des AAT-Proteins, welches aus aufgereinigtem Spenderblut gewonnen wird, verzögert werden. Die Substitutionstherapie wurde bisher kontrovers diskutiert. In Deutschland ist die Therapie im Gegensatz zu Großbritannien seit Jahrzehnten zugelassen, jedoch nur für Patienten mit mittelgradig eingeschränkter Lungenfunktion (forcierte exspiratorische Einsekundenkapazität [FEV_1] 35 – 60 % des Sollwertes) [3].

Klinische Relevanz

In Anbetracht der wohl hohen Anzahl an undiagnostizierten AATM-Fällen, sollten behandelnde Ärzte immer an diese Erkrankung denken. Die Diagnostik ist relativ einfach.

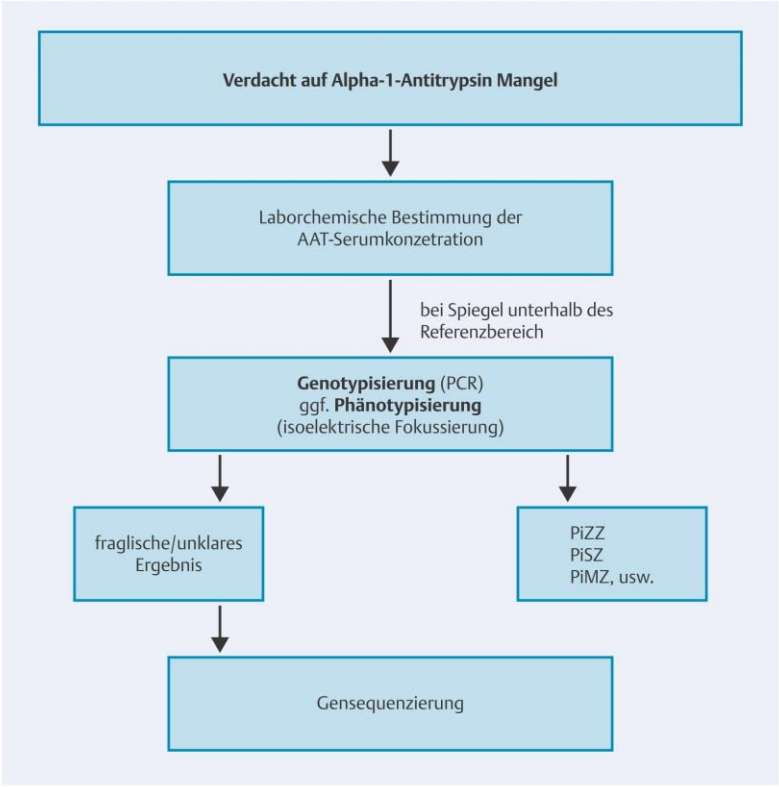

Abb. 1 Diagnostisches Vorgehen bei Verdacht auf Alpha-1-Antitrypsin-Mangel (AAT: Alpha-1-Antitrypsin; PiZZ, PiSZ, PiMZ: verschiedene Genotypen).

CT-Densitometrie zur AAT-Substitutionstherapie

Bisher gab es nur wenige groß angelegte prospektive, randomisierte Doppelblindstudien zur Substitutionstherapie. Aufgrund der Seltenheit der Erkrankung und der langsamen Krankheitsprogression ist es schwierig, anhand der Lungenfunktion (FEV_1) und der Diffusionskapazität (DLCO) den Verlauf der Erkrankung statistisch signifikant zu erfassen. Nicht in allen Studien, in denen die FEV_1 und DLCO als Endpunkte gewählt wurden, gelang es, einen signifikanten Nutzen der Substitutionstherapie zu belegen [5, 6]. Mit der Etablierung der Lungendichtemessung (CT-Densitometrie) konnte eine sensitivere Methode zur Abschätzung der Krankheitsprogression bei Lungenemphysem angewandt werden [5, 7–8]. In den letzten Jahren fand dieses Verfahren in zahlreichen Studien Verwendung [4, 9–11]. Bei dieser Methode wird die Abschwächung der Röntgenstrahlung bei Durchtritt durch das Lungengewebe als Maß für dessen Dichte herangezogen. Dieses Verfahren wurde in der RAPID-Studie zur Quantifizierung des Therapieerfolges angewandt.

In der 2015 publizierten randomisierten und placebokontrollierten Doppelblindstudie RAPID [4] wurden 180 AATM-Patienten mit AAT-Serumspiegel <11 µM in insgesamt 13 Ländern untersucht. 93 Patienten erhielten eine intravenöse Substitutionstherapie, 87 Patienten erhielten Placebo-Infusionen. Es konnten signifikante Vorteile für die Substitutionstherapie im Vergleich zu Placebo gefunden werden. PiZZ-AATM-Patienten mit intravenöser Gabe von 60 mg/kg AAT pro Woche zeigten in der zweijährigen Beobachtungszeit CT-densitometrisch (gemessen bei totaler Lungenkapazität [TLC]) einen verminderten Verlust an Lungendichte.

Die Daten der RAPID-Studie sprechen dafür, dass die Substitutionstherapie in der Lage ist, das Fortschreiten des Emphysems zu verlangsamen. Zwischen Verum- und Placebogruppe war jedoch kein Unterschied bezüglich FEV_1, Diffusionskapazität (DLCO), Exazerbationsrate, körperlicher Leistungsfähigkeit oder Lebensqualität zu finden. Eine Post-hoc-Analyse konnte zeigen, dass höhere therapeutische AAT-Spiegel mit einem verminderten Verlust an Lungendichte einhergehen. Weitere Studien müssen nun prospektiv untersuchen, ob eine höher dosierte AAT-Substitutionstherapie zu einem besseren Therapieerfolg führt. Die Ergebnisse geben Hinweise für einen Vorteil einer frühen Einleitung der Substitutionstherapie.

In die RAPID-Studie wurden nur Patienten mit einer moderat eingeschränkten Lungenfunktion (FEV_1 35–70% des Sollwertes) eingeschlossen. Inwiefern Patienten mit starker Beeinträchtigung der Einsekundenkapazität (FEV_1 <35% des Sollwertes) oder mit geringer Beeinträchtigung (FEV_1 >70% des Sollwertes) von einer Substitutionstherapie profitieren, bleibt offen. Hier müssen weitere Studien die nötigen Daten liefern.

Klinische Relevanz

Die aktuellen Daten der RAPID-Studie belegen den Nutzen der Substitutionstherapie. Die Ergebnisse legen nahe, dass sowohl die Höhe des therapeutischen AAT-Blutspiegels als auch die frühe Einleitung einer Therapie einen positiven Effekt auf den Krankheitsverlauf haben.

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