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Individualized lung function trends in alpha-1-antitrypsin deficiency: a need for patience in order to provide patient centered management?

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Background: Chronic obstructive pulmonary disease (COPD) is characterized by fixed airflow obstruction and accelerated decline of forced expired volume in 1 second (FEV_1). Alpha-1-antitrypsin deficiency is a genetic cause of COPD and associated with more rapid decline in lung function, even in some never smokers (NS) but the potential for individualized assessment to reveal differences when compared to group analyses has rarely been considered.

Methods: We analyzed decline in post-bronchodilator FEV_1 and gas transfer (% predicted) over at least 3 years (mean= 6.11, 95% CI 5.80–6.41) in our unique data set of 482 patients with alpha-1-antitrypsin deficiency (PiZ) to determine individual rates of decline, implications for prognosis, and potential clinical management.

Findings: There was a marked variation in individual rates of FEV_1 decline from levels consistent with normal aging (observed in 23.5% of patients with established COPD, 57.5% of those without) to those of rapidly declining COPD. Gas transfer did not decline in 12.8% of NS and 20.7% of ex-smokers with established COPD (33.3% and 25.0%, respectively, for those without COPD). There was no correlation between decline in gas transfer and FEV_1 for those with COPD, although a weak relationship existed for those without (r=0.218; P<0.025).

Conclusion: These data confirm differing individual rates of lung function decline in alpha-1-antitrypsin deficiency, indicating the importance of comprehensive physiological assessment and a personalized approach to patient management.

Keywords: alpha-1-antitrypsin deficiency, COPD, emphysema, lung function

Introduction

Chronic obstructive pulmonary disease (COPD) is a slowly progressive and destructive condition diagnosed by an impaired forced expired volume in 1 second (FEV_1) expressed as a ratio of the total forced expired volume (forced vital capacity, FVC). The FEV_1 has long been regarded as the most important physiological parameter because it relates to health status and respiratory as well as all-cause mortality.[1–3] Thus, short-term improvement and/or stabilization of COPD progression (as determined by the FEV_1) remain a long-term aim of current and future therapeutic development. In health, FEV_1 is influenced by age, sex, height, and ethnicity, and all factors are taken into account to provide a normal range and, by inference, identification of "abnormality" throughout life. At diagnosis, patients' results are placed in context of this normal range, and FEV_1 values are expressed as "% predicted".[4] At diagnosis, % predicted reflects historical progression and not future progression because the starting baseline is unknown, and smoking cessation, for instance, may lead to subsequent disease stabilization. The progressive decline in FEV_1 has conventionally been assessed as mL/year and, in

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general, patients with COPD have a more rapid decline than "usual." Decline is a feature of natural aging and the reduced FEV_1 of COPD has led to the concept of COPD reflecting an "accelerated ageing" process.[5] However, recent cohort studies have highlighted that the decline in FEV_1 in COPD differs between subjects, ranging from none to substantial annual loss.[6–8] This has led to categorization of some patients as "rapid decliners" although this characterization is determined by arbitrary cutoff points.

The concept of accelerated decline is particularly true in alpha-1-antitrypsin deficiency (AATD), which is a recognized genetic predisposition to COPD characterized by emphysema and more rapid disease progression than in nondeficient COPD due to the poorly controlled release of tissue damaging proteases.[9] Observational studies have suggested that in AATD decline in FEV_1 can be partly modified by regular augmentation of circulating AAT.[10–12] However, it is not clear whether this is indicated to prevent physiological progression in all individuals, as smoking cessation alone can stabilize FEV_1 decline[13] and subsequent individual differences are unknown. Nevertheless in many countries, AAT augmentation is the standard therapy to retard emphysema progression and stabilize lung function.[14]

Because of this uncertainty and the lifelong nature of augmentation therapy members of the Alpha-1-antitrypsin International Registry proposed a pragmatic approach based on physiological decline expressed as change in % predicted.[15] The reasoning for this is described in detail elsewhere;[15] a key point is that using % predicted accounts for age-related deterioration, such that if the % declines then the individual is deteriorating faster than normal aging, whereas a value in mL/year for FEV_1 is unable to separate people declining normally from those with an excessive decline. This approach might be critical for health systems to adopt in order to maximize the benefit from augmentation, by restricting to those with greatest potential to benefit. The present study explores the implications of this approach using unique data collected prospectively as part of the ADAPT (Antitrypsin Deficiency Assessment and Program for Treatment) registry of AATD patients never treated with augmentation therapy.

Methods

All patients referred to the ADAPT program who had the PiZ phenotype (n=482) were studied providing at least four annual lung function data points were available for analysis (average 5.92: 95% confidence interval [CI] 5.67–6.17 data points collected over an average of 6.11 years [95% CI 5.80–6.41]). Augmentation therapy is not available in the UK, but any patient who had received augmentation therapy or any other potential disease modifying therapy as part of a previous clinical trial was excluded from the analysis. The study was approved by the South Birmingham Local Research Ethics Committee (LREC 3359), and all patients gave written informed consent.

All the patients were seen and assessed at the Birmingham center, for post bronchodilator lung function testing, including measurement of lung volumes and gas transfer (DLco and Kco), all of which were performed according to accepted guidelines.[16] In addition, we documented demographics including smoking history and current status, quality of life, exacerbation history and drug history as described previously.[17] Index cases were defined as those tested because of presentation with respiratory symptoms. Nonindex patients were those identified through family screening. For the purposes of the current paper, the presence of COPD was defined as subjects with a post-bronchodilator FEV_1/FVC ratio $<70\%$.

Decline in lung function was determined by the change in % predicted for age, sex, height, and ethnicity using published equations[18] and linear regression determined for all annual data points (provided ≥ 4) for each patient and expressed as change in % predicted/year. Results were divided into those whose lung function decline (either FEV_1 or gas transfer adjusted for effective alveolar volume (Kco) was consistent with normal aging (change $<-0.1\%$ predicted per year), slow (-0.1% to $<-0.5\%$), moderate (-0.5% to $<-1.0\%$), and rapid decline ($>-1.0\%$) as described previously.[15]

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics version 21.0.0.0 for windows (IBM Corporation, Armonk, NY), stratifying for the presence of COPD. Chi-squared analysis was used to determine any differences between and across groups for categorical data and the Mann–Whitney *U*-test was used for all comparisons of differences between groups for continuous data as it was nonparametric in distribution. The Kruskal–Wallis test was used to determine differences across groups for continuous data (statistical significance taken as $P<0.05$). Multivariate analysis was performed using (backwards) stepwise linear regression with body mass index, age, sex, index status, smoking status (ex/never smokers), and inhaled therapy (combination, LAMA, ICS) taken into account to determine any factor that related to the % predicted decline.

Results

Demographic differences

The characteristics of the cohort are shown in Tables 1 and 2. Overall the PiZ non-COPD patients consisted of more never smokers, less index patients, and more females compared to PiZ patients with COPD ($P<0.0001$ for all comparisons). The non-COPD group consisted of more patients with no FEV_1 decline and conversely consisted of less patients with rapid decline than the group with established COPD ($P<0.0001$ for all comparisons). These data confirmed many prior associations of FEV_1 decline in AATD,[17] including a difference in the prevalence of bronchodilator reversibility between slow (22.4% of patients) and rapidly declining individuals (33.0% of patients; $P<0.024$). However, the decline rates for gas transfer were similar between the non-COPD group and the group with COPD ($P>0.25$ for all rates) and were not associated with factors previously shown to relate to FEV_1 decline (eg, bronchodilator reversibility, $P>0.40$). For the PiZ non-COPD group, no baseline demographic feature predicted the rate of decline of gas transfer, although rapid decline in FEV_1 was a feature of those with lower baseline FEV_1/FVC ratio and lower gas transfer compared with those with no decline ($P=0.003$ and 0.004, respectively, Table 2).

Average demographic data for the two patient cohorts are shown together with the standard deviation and subject number analyzed for each feature. The proportion of subjects in each of the subgroups is shown in percentage. Statistical differences between patients with and without COPD (P) are shown.

Demographics are shown for the AATD subjects without COPD in each of the four FEV_1 decline groups. Any differences across groups and between the nondeclining group and those with rapid decline are shown (P) and significant values are highlighted. N/A indicates no statistics were applied since by definition ("Methods" section) the four groups did not overlap.

Demographic data are shown for the AATD subjects with established COPD in each of the FEV_1 decline groups. Statistical differences across groups and between the non- and rapid-decliner group are shown (P).

In the group with COPD, all were taking short-acting bronchodilators, and 68% were taking at least one other established long-acting bronchodilator (eg, LAMA, LABA/ICS). For the PiZ group with established COPD, rapid decline was more likely in those with a higher baseline FEV_1 and FEV_1/FVC ratio than those with no decline ($P<0.0001$ and $P=0.017$, respectively) as summarized in Table 3. Again, no

Table 1 Characteristics of the patients with and without COPD

Characteristics	**Non-COPD n=87**				**COPD n=395**				***P*-value**
	N	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	
Never smokers	59	67.8%			82	20.8%			**<0.0001**
Index patient	38	43.7%			353	89.4%			**<0.0001**
Female	56	64.4%			153	38.7%			**<0.0001**
Age	87		44.8	13.2	395		52.9	9.3	**<0.0001**
FEV_1 % predicted	87		113.4	15.7	395		53.1	21.9	**<0.0001**
FVC % predicted	87		115.5	16.6	395		109.4	22.4	**0.002**
FEV_1/FVC	87		82.9	7.2	395		39.0	12.7	**<0.0001**
TLco % predicted	47		87.1	21.6	247		61.4	18.1	**<0.0001**
Kco % predicted	87		89.4	18.4	394		62.8	18.0	**<0.0001**
RV % predicted	87		88.8	21.4	385		128.1	39.3	**<0.0001**
TLC % predicted	86		106.8	13.6	385		117.1	15.2	**<0.0001**
RV/TLC	86		27.4	8.6	385		36.5	8.7	**<0.0001**
FEV_1 % slope per year	87		–0.12	2.3	395		–1.14	1.8	**<0.0001**
Kco % slope per year	87		–1.06	2.1	377		–1.41	2.0	0.145
Distribution within FEV_1 decline groups									
FEV_1 group 1	50	57.5%			93	23.5%			**<0.0001**
FEV_1 group 2	5	5.7%			42	10.6%			
FEV_1 group 3	10	11.5%			59	14.9%			
FEV_1 group 4	22	25.3%			201	50.9%			
Distribution within Kco decline groups									
Kco group 1	25	28.7%			72	19.1%			0.259
Kco group 2	6	6.9%			30	8.0%			
Kco group 3	13	14.9%			60	15.9%			
Kco group 4	43	49.4%			215	57.0%			

Notes: TLco is overall gas transfer; Kco is gas transfer corrected for alveolar ventilation. % values indicate the proportion of each group with individual categorical characteristics. Significant *P*-values are given in bold.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second; FVC, forced vital capacity; SD, standard deviation; RV, residual volume; TLC, total lung capacity

Table 2 Characteristics of patients without COPD substratified by FEV_1 decline

Demographics for FEV_1 decline groups non-COPD																		
FEV_1 decline group	**Group 1 n=50**				**Group 2 n=5**				**Group 3 n=10**				**Group 4 n=22**				**Across all groups**	**Statistic groups 1 and 4**
	No decline (decline of <–0.1% predicted per year)				**Decline of –0.1 to <–0.5**				**Decline of –0.5 to <–1.0**				**Decline of at least –1.0**					
	N	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	***P*-value**	***P*-value**
Never smokers	34	48.0%			3	60.0%			6	60.0%			16	72.7%			0.882	0.688
Index patient	24	48.0%			2	40.0%			1	10.0%			11	50.0%			0.146	0.876
Female	33	66.0%			3	60.0%			6	60.0%			14	63.6%			0.980	0.846
Age	50		42.8	12.9	5		34.4	12.4	10		46.7	14.2	22		50.7	11.7	**0.031**	0.140
FEV_1 % predicted	50		110.0	15.6	5		118.6	10.2	10		117.9	17.1	22		117.8	15.4	0.344	0.142
FVC % predicted	50		110.4	16.9	5		115.6	11.8	10		122.2	17.8	22		123.9	12.2	**0.012**	**0.002**
FEV_1/FVC	50		84.4	7.4	5		87.8	5.7	10		81.0	5.8	22		79.2	5.8	**0.006**	**0.003**
TLco % predicted	27		92.0	21.8	2		89.1	21.5	3		76.0	13.8	15		80.2	21.7	0.315	0.145
Kco % predicted	50		93.3	18.1	5		84.8	12.8	10		91.6	21.4	22		80.5	16.3	**0.031**	**0.004**
RV % predicted	50		85.3	17.7	5		108.0	31.1	10		93.2	14.8	22		90.4	27.0	0.253	0.557
TLC % predicted	50		104.0	12.7	5		115.5	19.7	10		111.8	13.0	21		109.2	13.4	0.126	0.107
RV/TLC	50		26.2	6.7	5		26.8	8.9	10		27.4	6.4	21		30.5	12.6	0.543	0.153
FEV_1 slope mL/year	50		–28.2	31.6	5		–37.0	30.3	10		–43.9	16.2	21		–105.1	49.5	N/A	N/A
FEV_1 % slope per year	50		1.3	1.3	5		–0.3	0.1	10		–0.70	0.1	22		–3.1	2.0	N/A	N/A
Kco % slope per year	50		–0.9	2.0	5		–1.4	1.1	10		–1.47	2.5	22		–1.1	2.4	0.956	0.883
Distribution within Kco decline groups																		
Kco group 1	15	30.0%			0	0.0%			2	20.0%			8	36.4%			0.166	0.799
Kco group 2	2	4.0%			2	40.0%			1	10.0%			1	4.5%				
Kco group 3	9	18.0%			0	0.0%			2	20.0%			2	9.1%				
Kco group 4	24	48.0%			3	60.0%			5	50.0%			11	50.0%				

Notes: TLco is overall gas transfer; Kco is gas transfer corrected for alveolar ventilation. % values indicate the proportion of each group with individual categorical characteristics. Significant *P*-values are given in bold.
Abbreviations: COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV_1, forced expired volume in 1 second; N/A, not available; SD, standard deviation; RV, residual volume; TLC, total lung capacity.

Table 3 Characteristics of patients with COPD substratified by FEV_1 decline

Demographics for FEV_1 Decline Groups COPD																		
FEV_1 decline group	**Group 1 n=93**				**Group 2 n=42**				**Group 3 n=59**				**Group 4 n=201**				**Across all groups**	**Statistic between groups 1 and 4**
	No decline (decline of <−0.1% predicted per year)				**Decline of −0.1 to <−0.5**				**Decline of −0.5 to <−1.0**				**Decline of at least −1.0**					
	N	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	***P*-value**	***P*-value**
Never smokers	19	20.4%			2	4.8%			9	15.3%			52	25.9%			**0.013**	**0.311**
Index patient	85	91.4%			40	95.2%			53	89.8%			175	87.1%			0.382	0.280
Female	43	46.2%			14	33.3%			20	33.9%			76	37.8%			0.337	0.171
Age	93		54.1	8.6	42		50.6	8.0	59		52.5	8.4	201		53.0	10.0	0.193	0.456
FEV_1 % predicted	93		50.5	24.8	42		41.5	17.2	59		47.8	19.1	201		58.3	20.8	<**0.0001**	<**0.0001**
FVC % predicted	93		107.1	24.1	42		98.1	18.4	59		104.0	20.6	201		114.5	21.6	<**0.0001**	**0.004**
FEV_1/FVC	93		37.7	13.8	42		34.3	11.6	59		36.9	12.1	201		41.2	12.1	**0.001**	**0.017**
DLco % predicted	61		61.3	19.7	20		57.1	20.5	37		62.6	17.9	132		61.8	17.3	0.722	0.788
Kco % predicted	92		64.6	19.2	42		62.4	19.0	59		66.2	19.1	201		61.2	16.8	0.265	0.203
RV % predicted	89		126.4	39.4	42		147.9	48.1	57		137.5	34.5	199		121.9	37.1	**0.001**	0.295
TLC % predicted	89		116.2	14.8	42		119.2	17.7	57		117.2	12.7	199		117.1	15.7	0.852	0.822
RV/TLC	89		37.2	8.8	42		40.3	10.1	57		38.8	7.1	199		34.7	8.4	<**0.0001**	**0.010**
FEV_1 slope mL/year	93		11.2	32.3	42		−22.4	10.6	59		−36.3	8.2	201		−86.2	54.7	N/A	N/A
FEV_1 % slope per year	93		0.9	1.2	42		−0.3	0.1	59		−0.8	0.1	201		−2.4	1.4	N/A	N/A
Kco % slope per year	89		−1.3	1.8	41		−1.2	1.5	58		−1.58	1.8	189		−1.5	2.2	0.709	0.730
Distribution within Kco decline groups																		
Kco Group 1	16	18.0%			10	24.4%			8	13.8%			38	20.1%			0.633	0.789
Kco Group 2	8	9.0%			5	12.2%			5	8.6%			12	6.3%				
Kco Group 3	14	15.7%			5	12.2%			6	10.3%			35	18.5%				
Kco Group 4	51	57.3%			21	51.2%			39	67.2%			104	55.0%				

Notes: TLco is overall gas transfer; Kco is gas transfer corrected for alveolar ventilation. % values indicate the proportion of each group with individual categorical characteristics. Significant *P*-values are given in bold.
Abbreviations: COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV_1, forced expired volume in 1 second; N/A, not available; SD, standard deviation; RV, residual volume; TLC, total lung capacity.

demographic features identified those with differing rates of gas transfer decline.

Of the 482 patients with sufficient data for analysis, 27 (5.5%) were current smokers at baseline assessment and most ceased smoking during data collection; hence, analysis of the impact of current smoking on decline could not provide meaningful data, and such patients were excluded from analysis.

Decline in lung function

Decline is summarized in Tables 2 (non-COPD subjects) and 3 (COPD patients). For the 87 patients without established COPD, 50 (57.5%) showed no excessive decline in FEV_1, whereas five (5.7%), ten (11.5%), and 22 (25.3%) showed slow, moderate, and rapid decline, respectively. The decline rate was similar for the slow moderate and rapid decline groups of never and ex-smokers. The average rapid decline for the ex-smokers (n=6) was greater (–4.17% predicted/year, standard deviation ±3.36) than the 16 never smokers (–2.64±1.00) although not statistically significant. The rapidly declining FEV_1 group of the six ex-smokers however had a more rapid decline in gas transfer than the 16 never smokers (–2.94±1.81% predicted/year vs –0.35±2.16% predicted/year; P=0.022). For the COPD patients (ex- and never smokers) 93/395 (23.5%) showed no decline in FEV_1% predicted. Forty-two (10.6%) showed a slow decline (–0.1 to <–0.5% predicted/year), 59 (14.9%) showed a moderate decline (–0.5 to <–1.0% predicted/year), and 201 (50.9%) showed a rapid decline (>–1.0% predicted/year). There was no significant difference in decline rate between never and ex-smokers. However, the proportion of ex-smokers and rapid and non-decliners differed between those with and without COPD as well as at different stages of COPD severity defined by the FEV_1.[4] These data are summarized in Figures 1 and 2, respectively.

There was a significant but weak correlation between the declines in gas transfer and FEV_1 in the patients without COPD (r=0.218; P<0.025). However, there was no correlation in AATD patients with established COPD (r=0.008; P=not significant) indicating that progression in these two physiological parameters is generally independent (Figure 3).

The decline rates for gas transfer in the PiZ COPD and non-COPD patients are summarized in Tables 2 and 3, respectively. In general 12.8% of COPD never smokers (n=81 where gas transfer was obtained for three or more consecutive years) had no decline in gas transfer with 7.7%, 20.5%, and 59.0% showing slow, moderate, or rapid decline, respectively (equivalent, on average, to –0.30%±0.12% predicted, –0.77%±0.13% predicted, and –2.56%±1.69% predicted,

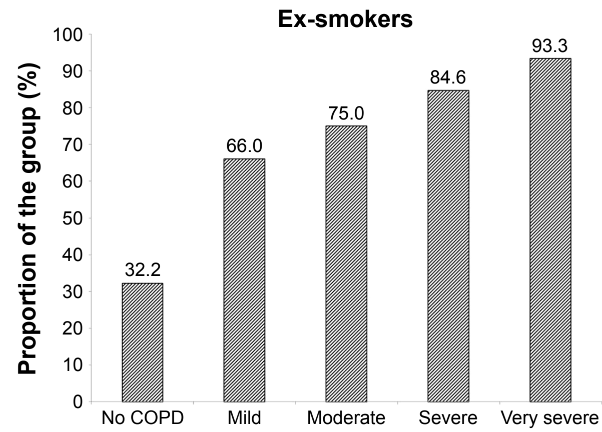

Figure 1 The proportion of patients who are ex-smokers.
Notes: The bar chart shows the proportion of those without COPD and those with different severity stages of COPD as defined by GOLD[9] who are ex-smokers.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic Obstructive Lung Disease.

respectively). Data for the ex-smokers (n=302) were similar with 20.7% showing no decline and 8.0%, 14.7%, and 56.5% showing slow, moderate, and rapid decline, respectively.

For those without COPD, 33.3% of the never smokers had no excessive decline in gas transfer with 3.5%, 18.6%, and 47.5% showing slow, moderate, and rapid decline, respectively. These data were again similar for the ex-smokers (25.0%, 14.3%, 7.1%, and 53.6% showing no, slow, moderate, or rapid decline, respectively).

Predicting progression through COPD severity stages

COPD is usually staged by the degree of impairment of FEV_1 expressed as a % predicted.[4] Cross-sectional measurement

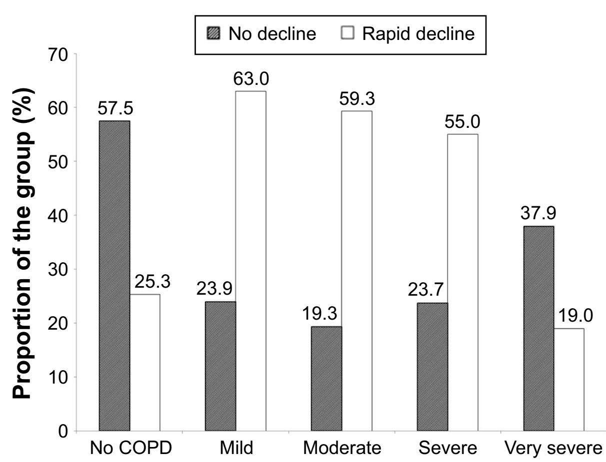

Figure 2 The proportion of subjects showing no decline or rapid decline in FEV_1.
Notes: The bar chart shows the degree of decline in FEV_1, categorized as no decline or rapid decline, in those without COPD and those with different severity stages of COPD.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second.

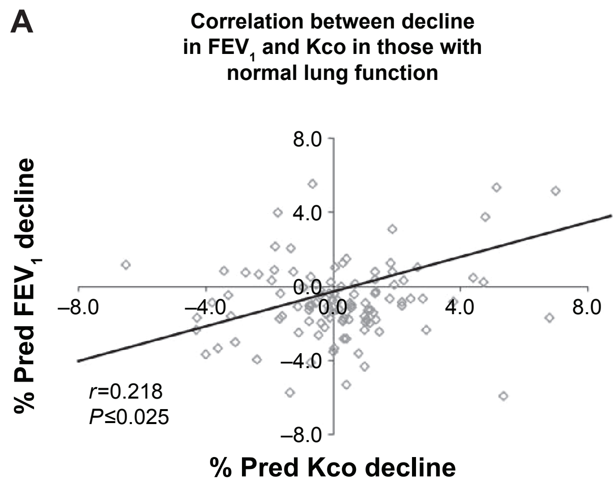

Figure 3 The relationship between the decline in FEV_1 and Kco.
Notes: The figure substratifies correlations between FEV_1 and Kco values in individual patients without (**A**) and with (**B**) established COPD. The correlation coefficient (*r*) is shown for both the groups with its significance (*P*). In both the graphs, the horizontal axis goes through the point of no decline in FEV_1, such that those points lying below the line have worsening FEV_1, while those above it have shown an improvement. Similarly the vertical axis passes through the point of no decline in Kco, such that those points lying to the left are deteriorating, while those to the right are not. The four quadrants therefore represent decline in both FEV_1 and Kco (bottom left), decline in Kco alone (upper left), decline in FEV_1 alone (bottom right), and decline in neither measure (upper right). Kco is gas transfer corrected for alveolar ventilation.
Abbreviations: % pred, % predicted; COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second.

does not provide historical evidence of decline since baseline starting point is unknown and neither is any influence of previous smoking. The rate of decline quantified here (for an individual) has to relate to the point of patient acquisition but would permit a general observation and prediction of the time needed to develop moderate (FEV_1 50%–80% predicted), severe (FEV_1 30%–50% predicted), and very severe (FEV_1 <30% predicted) COPD, assuming decline is and remains linear for given individuals (as demonstrated in Figures 4 and 5).

To determine the relationship between progression determined over 3 years with four full data points and that seen over longer periods of time, we compared the decline determined by linear regression for 123 patients where both four and eleven annual data points were available. These data are summarized in Figure 6 showing a good correlation between the short- and long-term data. Using our criteria, the positive predicted value of a slow decliner determined over 3 years was 84.5% when compared to 11 years decline and that for rapid decliners was 58.8%.

Discussion

The data presented here provide unique information on the physiological natural history of an untreated population of AATD patients assessed and monitored in a single center with high quality control for all measurements. The data indicate that physiological decline differs between subjects at all stages of lung function impairment for both index and nonindex patients as well as never smokers and ex-smokers.

The data have several important implications for patient management and particularly the consideration of augmentation therapy which is both expensive and requires weekly infusions of AAT for life. The aim of such therapy is to slow down or prevent progression of lung disease and is prescribed for AATD patients who have never smoked or who have stopped smoking. At present, the indications are generally restricted to those patients with an FEV_1 between 35% and 60% predicted (the "severe" COPD stage). This is based on the observation that a statistically significant slower decline in FEV_1 was observed in this physiological range of subjects who had received augmentation therapy but not at higher or lower levels in the National Heart Lung and Blood Institute observational study.[14] Whereas the observation is partly informative about the average effect on FEV_1 decline, overall it would not be expected to be effective/required if the FEV_1 were stable. Our data show that at all stages of COPD severity, defined by the FEV_1, there are patients who do not decline during the observational period as well as those who decline rapidly.

Our data, divided into patients within the widely recognized Global initiative for chronic Obstructive Lung Disease stages,[4] show that the proportion of rapid decliners (as defined here) differs with severity. However, there remains a significant proportion of individuals who decline less rapidly or not at all, at all stages of disease severity. In addition, the proportion of ex-smokers within each FEV_1 stage increases

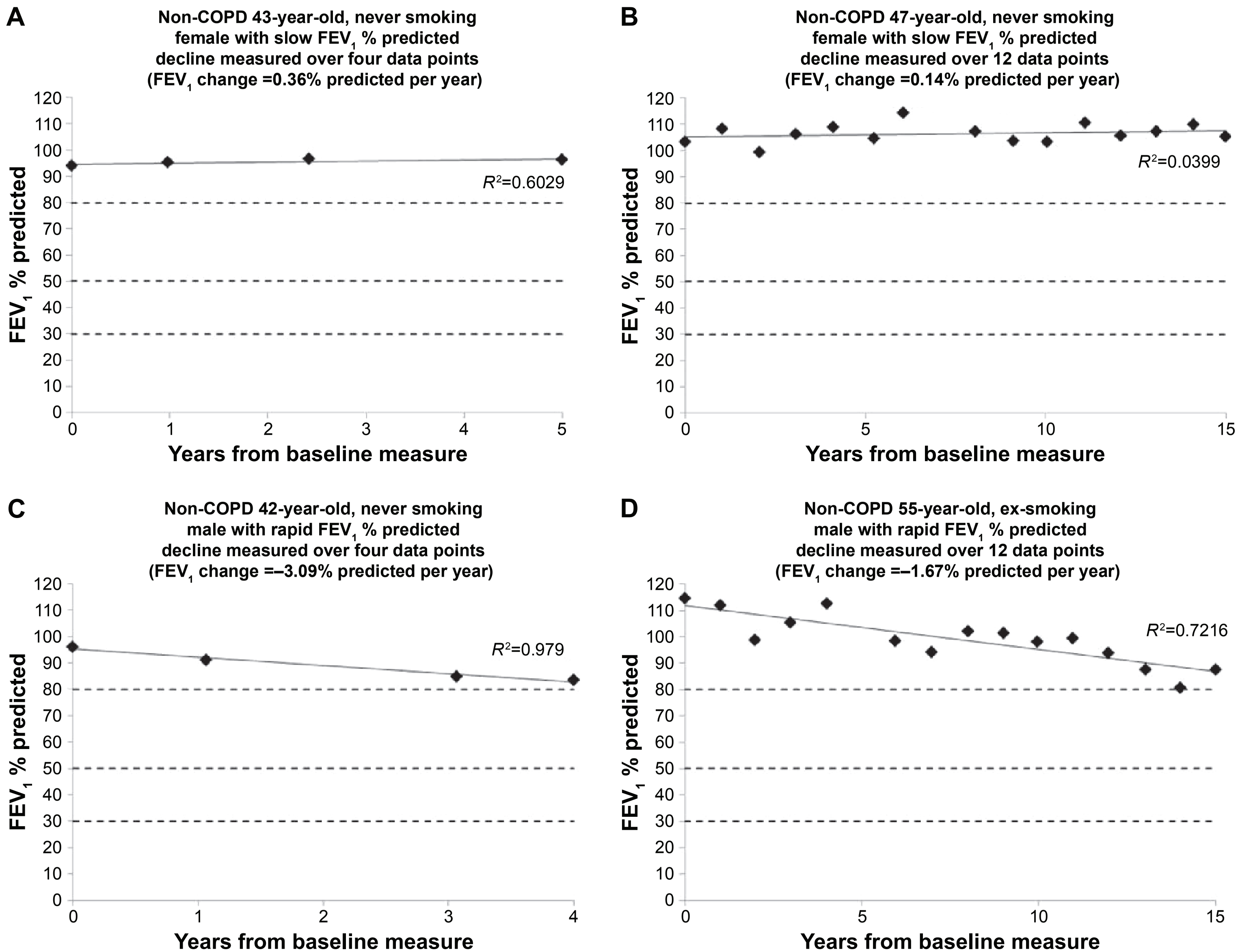

Figure 4 The decline in FEV_1 for individual patients without COPD.

Notes: Representative patients have been chosen to demonstrate the pattern of FEV_1 decline in (**A** and **B**) slow/no decline and (**C** and **D**) rapid decline. The similarity of the slope in patients followed over prolonged periods (**B** and **D**) to those followed over shorter periods (**A** and **B**) demonstrates that decline is linear in an individual over time, such that shorter periods might be used to determine longer-term prognosis.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second.

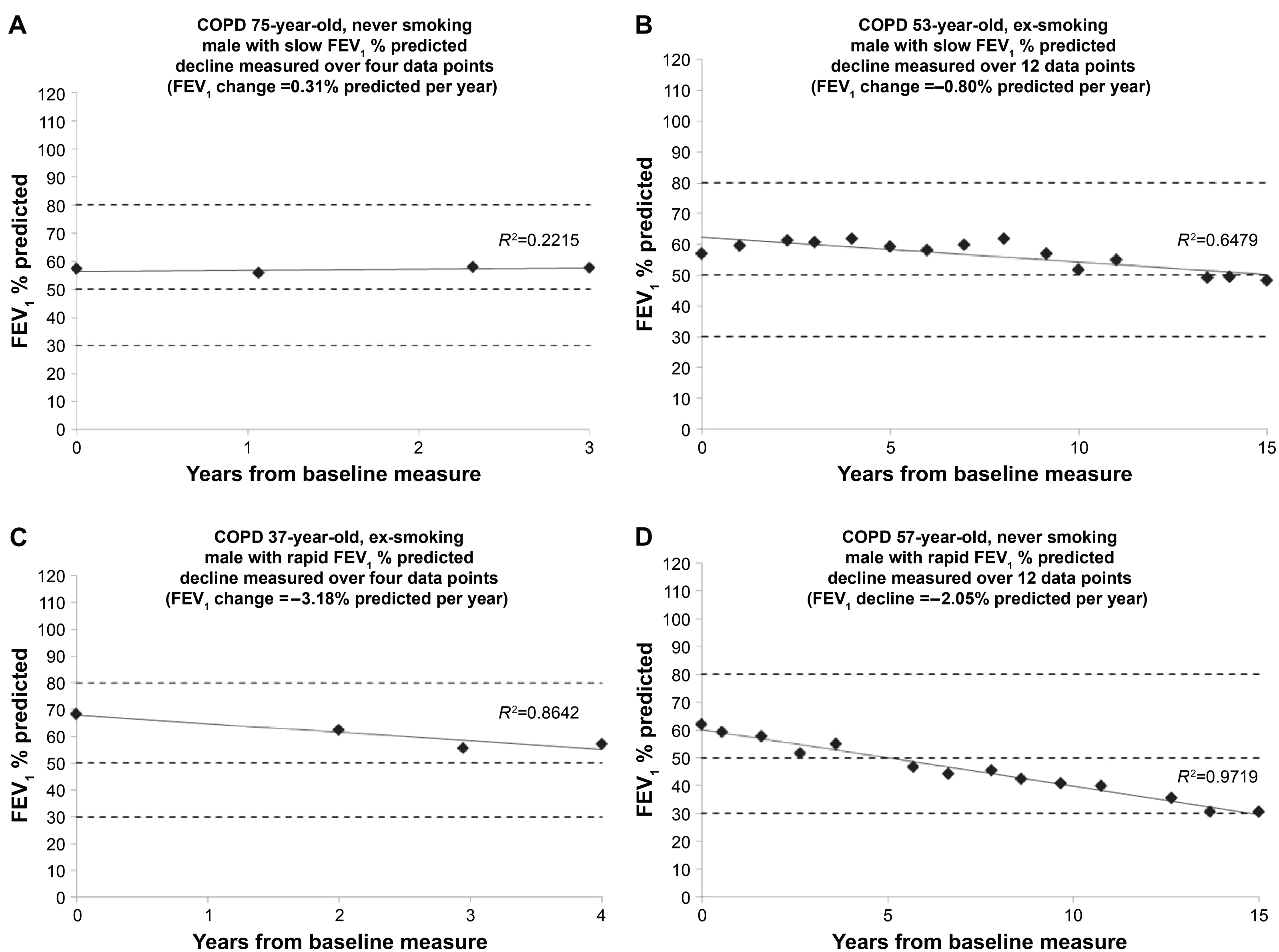

Figure 5 Decline in FEV_1 for individual patients with COPD.
Notes: This figure demonstrates the pattern of slow decline (**A** and **B**) and rapid decline (**C** and **D**) in patients with COPD. A linear pattern in any given individual was seen.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second.

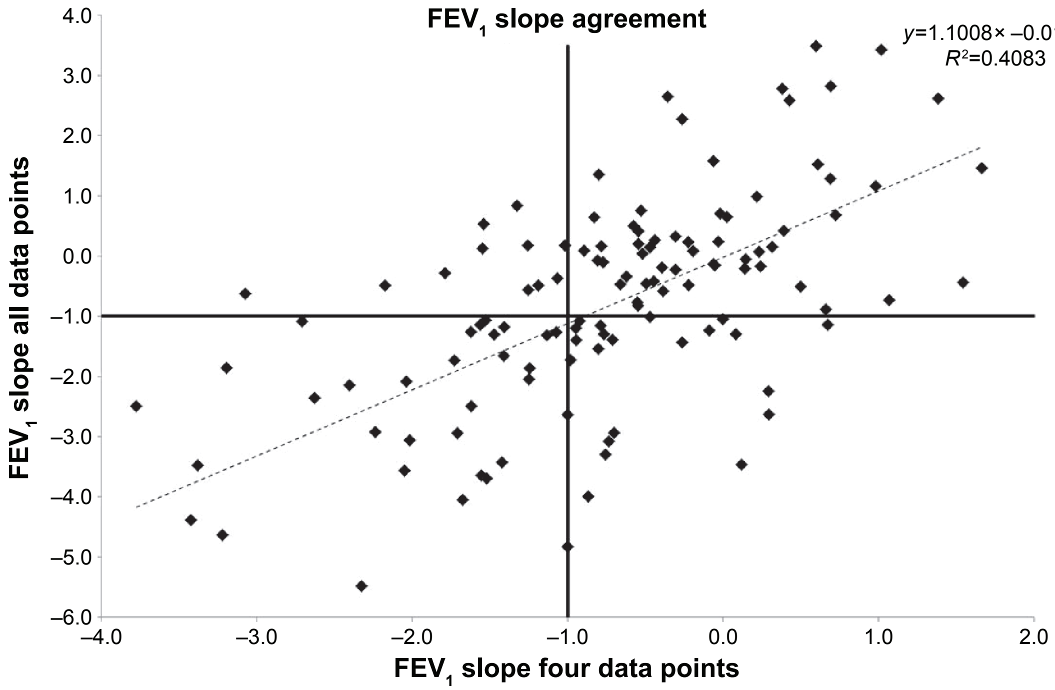

Figure 6 The degree of agreement between measures of FEV_1 decline.
Notes: The decline in FEV_1 determined by linear regression analysis is shown for patients in whom both four and eleven annual data points were available. The horizontal and vertical lines indicate the threshold of 1% predicted decline used here to delineate the rapid decliners. The regression equation and r^2 value is shown; there is a good relationship indicating that four data points may be adequate to determine longer-term prognosis.
Abbreviation: FEV_1, forced expired volume in 1 second.

with severity suggesting their decline while smoking was far more rapid than that after smoking cessation. Since never and ex-smokers generally decline at the same rate, the data explain (at least in part) why Stage 4 COPD which consists of virtually all (94%) ex-smokers has a slower decline compared with the less severe stages. Nevertheless, rapid and nondecliners are present at all stages of the disease process. In general, the lower the FEV_1 the greater the likelihood of death[19] and the need for transplantation. Thus, knowledge of FEV_1 decline will play a key role in decision making about augmentation therapy aimed to slow or stop decline in an individual patient. Furthermore, knowledge of decline may allow enrichment of patient cohorts for future studies by selecting rapid decliners and ensuring adequate power where physiological decline is the outcome.

Use of a patients' longitudinal data to decide about augmentation would have a number of impacts on clinical practice. In some patients, rapid decline might be apparent early in follow-up, in which case documenting this before treatment would provide a baseline to monitor the effects of augmentation.[20] In most there would be a delay of up to 3 years to make a decision about treatment, especially ex-smokers where precessation and subsequent decline may differ. The positive predictive value for identifying slow/nondecliners with this method would be 84.5% (Figure 6), indicating that with four annual data points, those in whom augmentation therapy would have less impact on FEV_1 decline can be identified with reasonable confidence. Conversely, the positive predictive value of identifying long-term rapid decliners with four annual data points is less (58.8%), which indicates little change over the initial 3-year period in a proportion who have a significant decline confirmed subsequently. Longer follow-up might ensure that such individuals obtained augmentation therapy at an appropriate later time point. Alternatively monitoring a more specific physiological measure of emphysema such as gas transfer may be as or more appropriate for decision making. Gas transfer relates to lung density, especially in the upper zones,[21] and this anatomical effect explains why the gas transfer decline is greatest late in the disease[17,19] as the classical basal emphysema becomes more apparent in the upper zones. This region of the lung, however, may be less responsive to augmentation therapy.[22] Furthermore, it does not relate to the FEV_1 decline except in early disease (Figure 1). Whether monitoring gas transfer decline can be an indicator for the need for augmentation therapy in the absence of an FEV_1 decline requires further study perhaps before and after the start of augmentation therapy.

It is possible that the eventual pool of patients eligible for augmentation could be extended. The identification of rapid decliners with initial lung function in the normal range, or with mild COPD, suggests that such individuals should also be considered for augmentation therapy, where current guidelines would not recommend this, as their FEV_1 is too well maintained. Interestingly the idea of earlier treatment in COPD to prevent decline is one that has also been raised in patients with COPD unrelated to AATD.[23]

In such patients, knowledge of the decline rate allows informed outcome prediction and earlier decision making about augmentation therapy even outside the current prescribing limits. This could have great potential societal and economic benefits, such as patients remaining in work.

Prevailing FEV_1 alone does not provide this information on an individual patient basis even in lifetime never smokers. Mild impairment in middle age may be perceived to reflect slow decline. However, since the initial FEV_1 at maturity is unknown, this could reflect both a slow decline for those whose FEV_1 started at the bottom of the normal range and a rapid decline for those who started at the top of the normal range. In addition ex-smokers, even with severe impairment, may stabilize their FEV_1. For these reasons, a period of observation of FEV_1 decline would appear mandatory before implementing augmentation therapy.

Knowledge of FEV_1 decline therefore allows both a projection of likely future progression[24] and prognosis and more informed confidence of the need and subsequent expected effects of augmentation therapy. Furthermore, the presence of rapid or nondecline can indicate patients who most (or least) require augmentation therapy to influence prognosis.

Clinical trials to demonstrate the efficacy of augmentation therapy have proven impractical with FEV_1 as a primary outcome. Indeed its sensitivity to change is low,[24] suggesting large numbers of patients are required over prolonged periods to confirm or refute efficacy. FEV_1 is however only a surrogate of the emphysema process and hence the acceptance of CT densitometry as an alternative outcome. This is far more sensitive to change,[25] is related cross-sectionally to lung physiology and health status[26] and mortality[27] and the decline in FEV_1 in longitudinal studies.[28,29] Longitudinal follow-up of density in our untreated patients also suggests that density decline relates to mortality.[30] Clinical trials using density decline as an outcome have been consistent in demonstrating benefit[31–33] and the recent adequately powered study alone has confirmed a treatment effect.[31] However, not all AATD patients show a decline in densitometry,[29,31] and our published data show that neither FEV_1 nor gas transfer measurement is capable of identifying all patients whose CT density is deteriorating. This implies that monitoring density decline might also be necessary for decision making, though benefit from serial scans identifying emphysema progression would need to be balanced against the requirement for specialist interpretation and repeated radiation exposure.

Conclusion

The data show that lung function decline in AATD differs between patients but that rapid decline is present in both patients with and patients without COPD. The decline determined for an individual, especially with respect to FEV_1, appears linear, permitting longer-term projection to be estimated particularly in ex-smokers (where the decline rate may have changed). This would allow identification of those more likely to need/benefit from augmentation therapy and also provide a means of assessing response to this by close subsequent monitoring.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

RAS and AMT have attended advisory board meetings for Grifols and CSL Behring. AMT has received noncommercial grant funding from CSL Behring and RAS has received noncommercial grant funding from Grifols and CSL Behring. The authors report no other conflicts of interest in this work.

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